Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

NOVEMBER--1960

Volume 10 - Number 11

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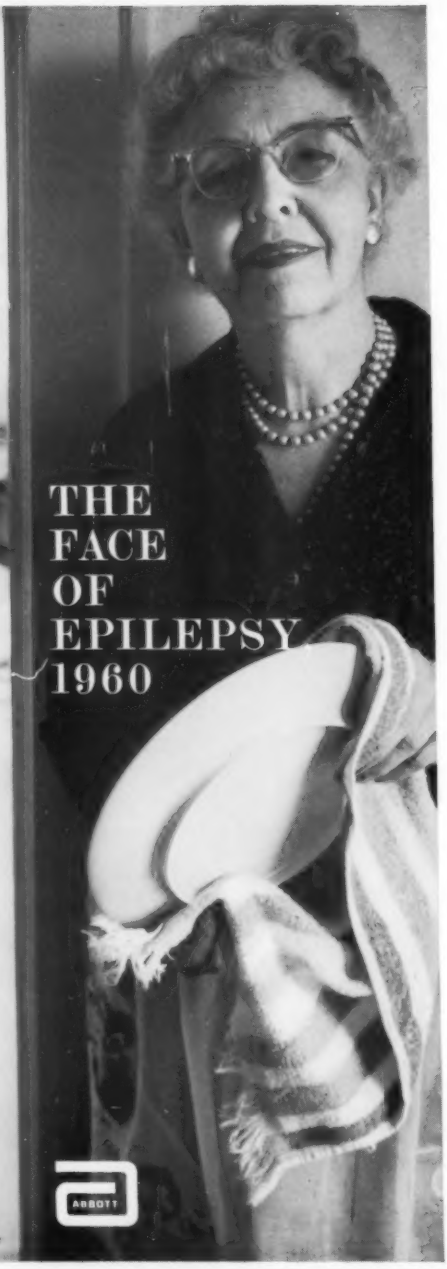

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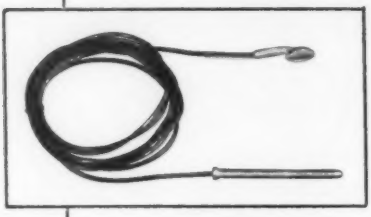

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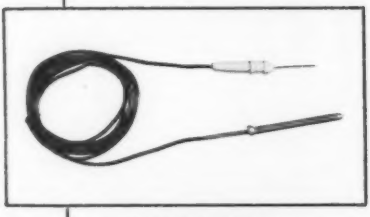

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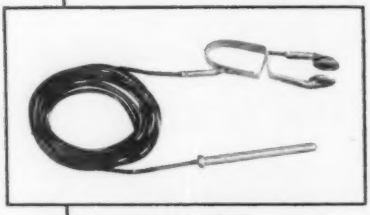

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INFORMATION FOR *Authors*

NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

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*Khakee, A., and Hess, G. F.: Mellaril in the Treatment of Chronically Disturbed Patients: With Special Reference to Reduced Extrapyramidal Complications, Am. J. Psychiat. 116:1030 (May) 1960.

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1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.

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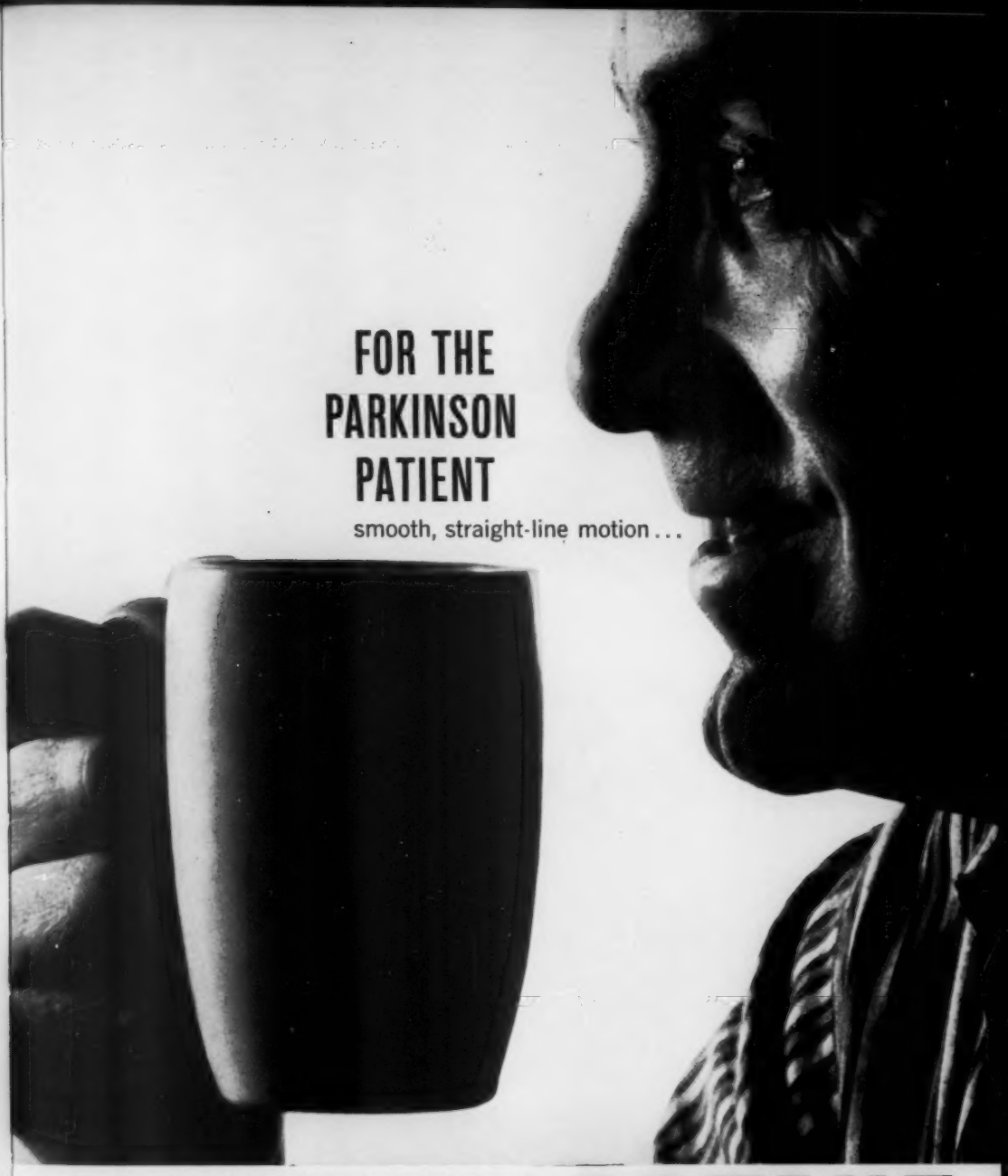

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1. Critchley, M.: British M. J. 2:1214 (Nov. 15) 1958.
2. Doshay, L. J.: Current M. Dig. 22:11 (Nov.) 1956.
3. De Jong, R. N.: J. Michigan M. Soc. 57:722 (May) 1958.

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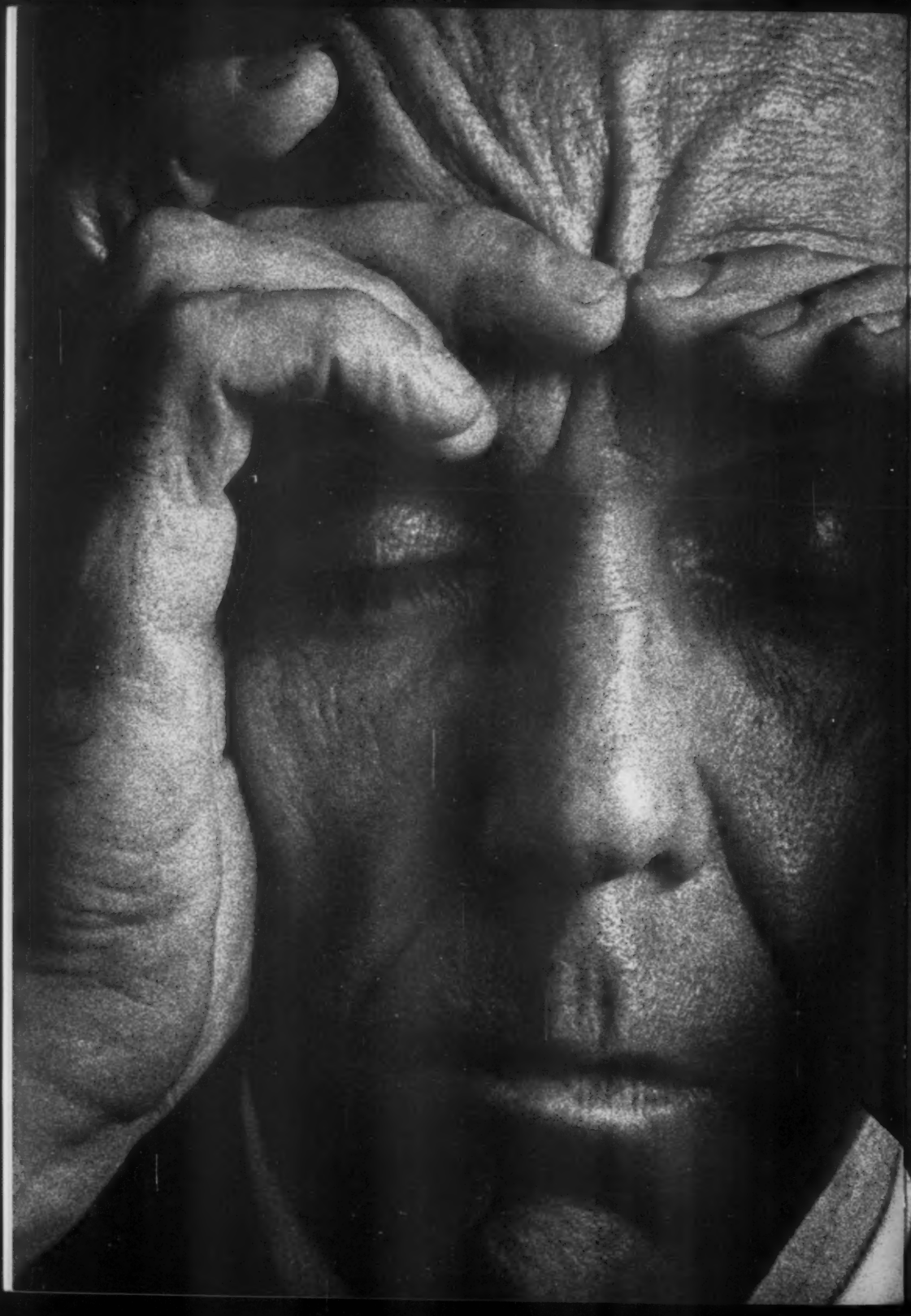

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1. Schwab, R. S. and England, A. C.: *J. Chron. Dis. 8*:488 (Oct.) 1958.
2. Schwab, R. S.: *Geriatrics 14*:545 (Sept.) 1959.
3. Doshay, L. J. et al.: *J.A.M.A. 160*:348 (Feb. 4) 1956.

PAR-GP03

Neurology Volume 10 • Number 11

Development and distribution of gross atherosclerotic lesions at cervical carotid bifurcation

Capt. Ralph E. Peterson, M.C., U.S.A.F.,
Kenneth E. Livingston, M.D., and Alfonso Escobar, M.D.

THE RECENT UTILIZATION of vascular surgical procedures for the relief of segmental obstruction in the cervical portion of the carotid artery[1–9] has increased the importance of information regarding the development and distribution of the underlying atherosclerotic lesions.

Because of its relative inaccessibility in routine autopsy examinations, the cervical carotid artery has, until recently, been considerably neglected in the analysis of pathologic alterations underlying "stroke" disabilities.[10–13] Anatomic studies demonstrate that the atherosclerotic lesion in the carotid is commonly maximal at the level of the cervical bifurcation,[14–18] and clinical data from arteriographic study reveal a surprising frequency of partial or complete obstruction at this site.[19–26] Because of the technical feasibility of surgical procedures in these vessels, obstructing lesions acquire particular interest and importance.

The present study was undertaken to obtain information regarding the localization and progression of the atherosclerotic process in this region; 123 carotid bifurcation specimens were studied from individuals ranging in age from 17 to 90 years, with a median age of 48. Specimens were divided into 3 groups according to age (Table 1). Both carotids were available for study in all but 15 individuals.

Specimens were removed, cleaned of excess connective tissue, and fixed in 10% formalin. Before the tissues hardened, the "normal" lumen contour was established by filling the segment with warm paraffin. Standard photographs of each specimen were made to permit measurements and comparisons. The gross external characteristics were recorded (Fig. 1). The approximate center of the bifurcation was established, and the proximal and distal arteries were transected 1 cm. from this point (Fig. 2). A thin cross section of each artery was taken at this level to permit measurements of lumen area (Fig. 3). The bifurcation segment was then split longitudinally to show internal detail and changes within the arterial wall (Fig. 4).

Gross evidence of atherosclerosis from minimal to severe was found in all specimens. The intensity of the lesion increased with age. Although surprising differences in the extent of

From the University of Oregon Medical School and Providence Hospital, Portland, and the Institute of Biology and Medicine, University of Mexico, Mexico City.

TABLE 1
123 CAROTID BIFURCATION SPECIMENS FROM PERSONS AGED 17 TO 90
Years Arranged in 3 Groups of Median Ages 30, 50, and 71 Years

Group	*Age limits (years)*	*Number of specimens*	*Median age*
I	40 and under	48	30
II	41 to 60	42	50
III	61 to 90	33	71

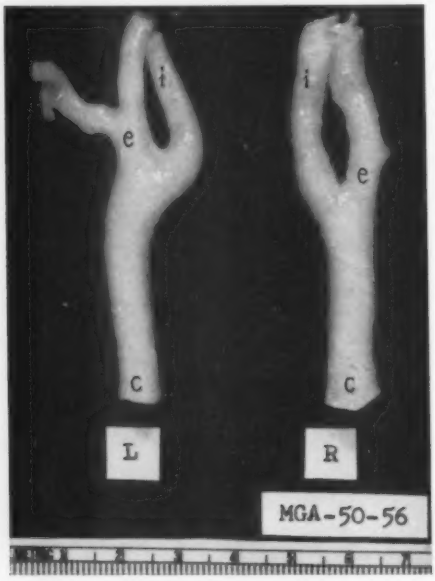

Fig. 1. Gross external characteristics of carotid bifurcation. c=common, i=internal, and e=external carotid arteries.

involvement of the right and left carotid in the same individual were sometimes encountered, no preponderance of change to either side was noted. The lesions appear first and are typically most severe at the level of bifurcation, next extending to the proximal wall of the internal and the distal wall of the common carotid. One of the most striking findings was the remarkable degree to which gross pathologic changes were restricted to the immediate zone of bifurcation, leaving the proximal and distal carotid segments essentially uninvolved (Fig. 5).

Planimeter measurements of the cross-section area of the common internal and external carotid arteries were made at a distance of 1 cm. from the center of bifurcation (Table 2).

Comparison of measurements in the 3 age groups indicates little change in the external carotid but substantial increase in size of the common and internal carotid. The common carotid doubles in cross-section area between 30 and 70 years, while the internal carotid increases more than three times during that interval. This relatively greater enlargement of the internal carotid is evident grossly in the ballooned appearance of its proximal segment, particularly noticeable in older specimens (Fig. 6). In younger specimens (Fig. 7), dilation is frequently absent or minimal, so that its enlargement appears to parallel aging and degenerative changes in the bifurcation zone.

While the cross-section areas of the 3 vessels were seldom equal on 2 sides, differences were not great and no preponderance of enlargement on either side was encountered (Table 3).

Although 15 specimens showed marked widening of the angle of carotid bifurcation (Fig. 6), the change did not appear directly related to age (Table 4). In 12 of the 15 specimens showing more than 50% increase in this angle (60° or greater), both right and left

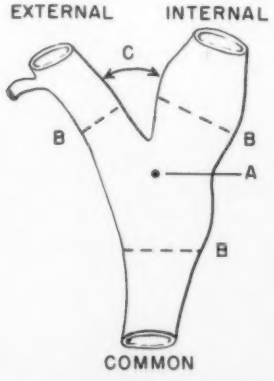

Fig. 2. Sites of measurement of bifurcation specimens. A=center of bifurcation; B=level of section 1 cm. proximal and distal to A; C=angle of bifurcation.

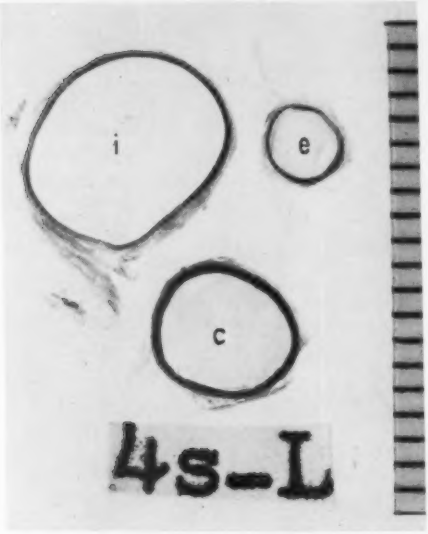

Fig. 3. Enlarged cross section of arteries 1 cm. from the center of the common carotid bifurcation, for measurement of lumen area. From person aged 70 years

Fig. 4. Longitudinal section of the bifurcation showing the internal surfaces and pathologic changes within the arterial wall. From person aged 46 years

TABLE 2
CROSS-SECTION AREA OF CAROTID LUMEN AT LEVELS 1 CM. FROM CENTER OF BIFURCATION

Group	*Lumen area in square millimeters*		
	Common carotid	*Internal carotid*	*External carotid*
I	16	9	9
II	26	16	10
III	34	34	12

TABLE 3
COMPARISON OF RIGHT AND LEFT CROSS-SECTION AREAS

Artery	*Right larger*	*Left larger*	*Equal size*
Common carotid	25	22	7
Internal carotid	25	26	3
External carotid	25	24	3

Fig. 5. Specimen from person 50 years old showing marked atherosclerosis at the level of bifurcation, with little involvement of the adjacent proximal and distal segments

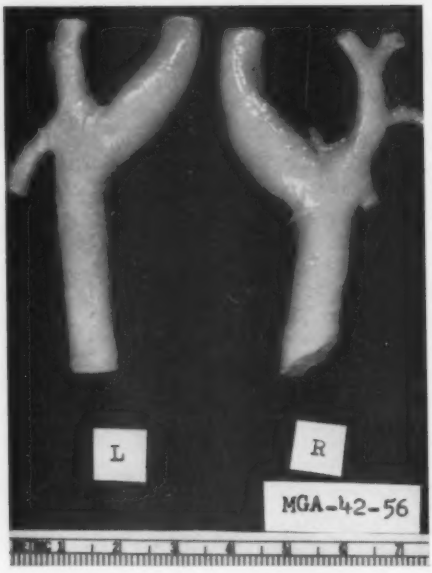

Fig. 6. Marked dilation of the proximal segment of the internal carotid from person aged 50 years. This is particularly noticeable in older specimens.

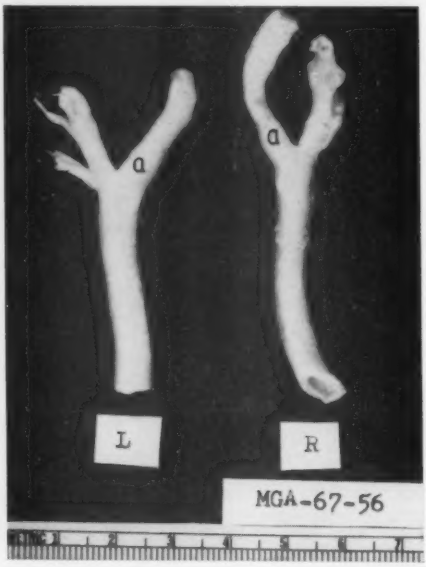

Fig. 7. Bifurcation specimens from person 17 years old, showing absent or minimal dilation (a) of the proximal segment of the internal carotid

carotids were involved. In 3 instances, striking unilateral widening (70° or greater) of the bifurcation was encountered while the opposite carotid angle remained "normal."

DISCUSSION

Obviously, many factors both known and presently unknown contribute to the pathologic alterations encountered in the cervical carotid bifurcation area. In this study, the most significant comparisons are probably those between the right and left carotids in the same individual because the variables of age, diet, physical and emotional activity, and metabolic, endocrine, and genetic patterns may be assumed to act equally on the two carotids. The anatomic arrangement of the carotid artery differs on the two sides, the left arising directly from the aorta with the cervical bifurcation closer to and more directly above the ventricle on this side. We had anticipated finding differences ascribable to this anatomic and mechanical asymmetry. However, we did not find any consistent lateralized difference in the extent of atherosclerotic involvement, dilation of the carotid vessels, or change in bifurcation angle.

Dilation of the vessels, particularly if segmental and irregular, and marked increase in bifurcation angle must create substantial disturbance in arterial flow which may adversely affect the distal circulation. Locally, increased turbulence producing eddy currents in which particulate cellular and molecular material subject the endothelial wall to more concentrated bombardment may accelerate the pathologic change. Further damaging effects may result from the concomitant relative stasis in portions of this area. The remarkable lack of atherosclerotic change in the straight unbranched

TABLE 4
COMPARISON OF CAROTID BIFURCATION ANGLE ACCORDING TO AGE

	Groups			Median
	I	II	III	
Bifurcation angle	43°	39°	40°	41°

segments of the common and internal carotid arteries in the presence of severe involvement of the bifurcation zone emphasizes the role of such mechanical factors. As changes in the subendothelial layers extend and nutrition of the vessel wall is impaired, the lesion may develop at an accelerated rate.

Included in this study are paired bifurcation specimens from 39 individuals of Mexican racial background, all having lived in the same institutional environment on a markedly restricted dietary regime. This group is relatively homogenous in terms of physical and emotional activity and metabolic, endocrine, and other factors. The group is homogenous in terms of nutritional status. Comparison of this group with other material in the study shows no qualitative differences in the topographic pattern of the lesions, the sequence of involvement, or the changes in vessel size and bifurcation angle. Quantitatively, the differences are not marked except in the fact that the atherosclerotic lesion, although extensive and advanced in age, remained confined to the arterial wall in this undernourished group without appreciable reduction of lumen, as was frequently encountered in other specimens studied. Since the problem of vessel obstruction at this level is of great clinical importance, a more detailed analysis of the lesions from this standpoint will be presented subsequently.

SUMMARY

A study of 123 specimens of the cervical carotid bifurcation area is presented.

Gross atherosclerotic lesions occur in this area by the third decade and progress with age.

The point of bifurcation is first involved, with subsequent extension of the lesion into the proximal portion of the internal and the distal portion of the common carotid.

The gross atherosclerotic lesion commonly remains restricted to the zone of bifurcation.

The common carotid proximal to the bifurcation and the internal carotid distal to the bifurcation show a marked increase in size with advancing age. Enlargement is most marked in the proximal internal carotid.

The angle of carotid bifurcation frequently widens markedly, usually bilaterally.

We found no tendency for changes in the bifurcation area to predominate on either side.

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Familial amyotrophic lateral sclerosis occurring in 4 generations

Report of a case

Lt. Joseph B. Green, M.C., U.S.N.R.

KURLAND and Mulder, in a series of reports,[1-4] have indicated that the amyotrophic lateral sclerosis symptom complex may represent a hereditary disorder. In addition to their studies of a familial type of the disease occurring in Micronesian natives, they collected 18 pedigrees from the world literature and added 6 more familial aggregations they identified from observations at the Mayo Clinic. An analysis of this information suggested a dominant mode of inheritance of the "motor system diseases," that is, amyotrophic lateral sclerosis, spinal muscular atrophy, and bulbar palsy. This present communication will describe a family of Pennsylvania Dutch extraction in which 7 cases of the amyotrophic symptom complex have occurred in 4 generations.

CASE HISTORIES

The patient or propositus, designated by the arrow in the figure, was a 33-year-old man who had noticed progressive weakness of the right hand for three months. He had begun to drop pencils and coins from the hand at the time of the initial visit. He had no paresthesias but did complain of occasional pain located near the right elbow. Significant past history revealed a diphtheritic infection at the age of 7. During World War II, he had sustained a superficial shrapnel injury resulting in a deformity of the right ear. Since that time, slight right facial weakness had persisted. The initial neurologic examination revealed the following: moderately severe atrophy of the intrinsic muscles of the right hand in both the ulnar and median distributions; fasciculations in the right brachioradialis muscle; and definite weakness of the deltoids, biceps, and triceps bilaterally but more marked on the right.

The deep tendon reflexes were barely obtainable in the upper extremities but were normally active in the lower limbs. Increased myotatic irritability of the shoulder girdle musculature was noted. No weakness, atrophy, or fasciculations of the muscles of the lower extremities were found. The plantar responses were flexor. No sensory deficit could be demonstrated.

Routine laboratory examinations, including hemogram, urinalysis, blood serologic test for syphilis, fasting blood glucose, and blood urea nitrogen, were all considered to be within normal limits. Roentgenograms of the chest, cervical spine, and skull were within normal limits, except for shrapnel fragments, subcutaneous in location, about the right ear. Examination of the cerebrospinal fluid disclosed clear fluid under a pressure of 12 cm. No cells were noted; the protein was 32 mg. per cent. The serologic test for syphilis was nonreactive, and the colloidal gold reaction was 0000000000. A myelogram was performed, and the dye was carried up to the foramen magnum. No abnormalities were visualized at fluoroscopy or on the roentgen films.

Electromyograms revealed evidence of diffuse lower motor neuron disease with fibrillation potentials obtained from virtually all musculature of the upper extremities and both gastrocnemii. During the following nine months, the patient had a downhill course with progressive atrophy and weakness of the mus-

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cles of both upper extremities and shoulder girdles, sternomastoids, and face. Most recently, he had a weak, nasal voice and a right extensor plantar response.

The patient's mother (III-6 in figure) died after an illness of fourteen months. She was seen by several physicians who concurred in the diagnosis of progressive spinal muscular atrophy. At the age of 37, she noted weakness of the toes of the left foot. The weakness progressed to involve first the entire left lower extremity and, eventually, both lower extremities. She ambulated on crutches for a time, then became bedridden. Evidently, her upper extremities and bladder were not affected.

Her sister (III-8), the propositus' aunt, died at the age of 36 of a similar disease. Weakness, first noted in the left foot, later involved both lower extremities and was associated with marked muscular wasting.

The maternal grandmother of the propositus (II-3) died at the age of 59. She suffered from a lingering illness characterized by progressive loss of bulbar functions. Phonation was lost, and swallowing became impossible. She died of inanition approximately one year after onset.

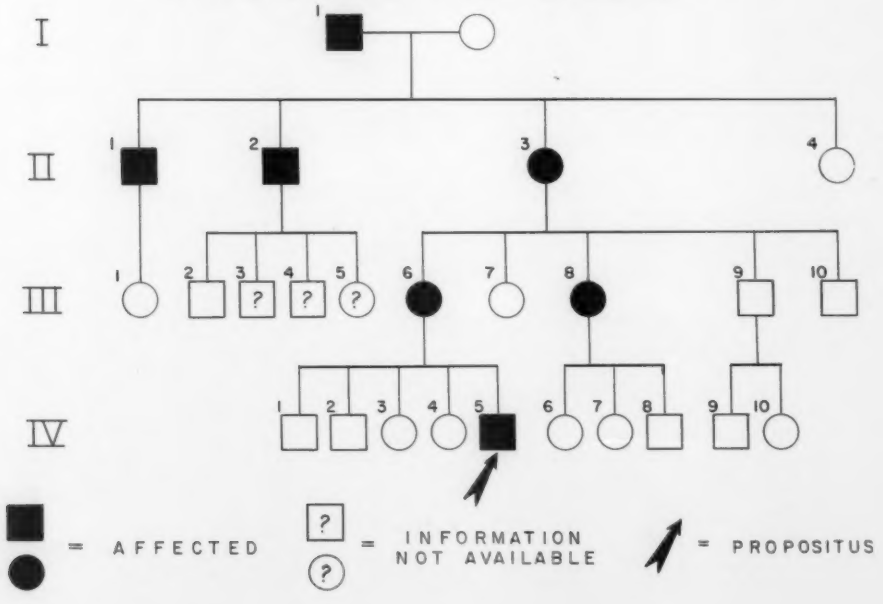
The propositus' 2 great-uncles (II-1, II-2) each died of a progressive muscular disease beginning in the hands. History is scanty, but, in each case, the illness is purported to have followed a "back or spine" injury.

The prospositus' maternal great-grandfather (I-1) was a physician of Pennsylvania Dutch extraction. He died at the age of 30 of a condition he had described as the "creeping paralysis." He indicated that the disease had been "in the family," but it cannot be determined whether on the paternal or maternal side. The affliction started in his hands, and it became necessary for his daughter to accompany him on his calls to measure and administer medications.

DISCUSSION

It is reasonable to suppose that the amyotrophic lateral sclerosis symptom complex existed in this family for more than 4 generations, because the first recorded victim, a physician, readily diagnosed his own illness as

Familial Amyotrophic Lateral Sclerosis in 4 Generations



familial. The mode of inheritance would seem to be dominant in this and most families reported, although Kurland and Mulder[3] have reported individuals with the disease whose parents were not affected.

In this family 3 varieties of "motor system disease" were represented; 1 woman died of progressive bulbar palsy, while 2 had clinical pictures compatible with progressive spinal muscular atrophy. At least 1 of the 4 stricken men, the propositus, evidenced a combination of anterior horn cell and pyramidal tract disease.

The pattern of the disease was strikingly similar in siblings of the same sex. The brothers II-1 and II-2 had almost identical illnesses beginning with weakness of the hands. The sisters III-6 and III-8 each had progressive weakness and atrophy beginning in the left foot. Their ages at onset differed by only two years. Thus, the clinical variety of the disease appeared to be linked to sex and age at onset. Indeed, the history of this family, as well as of others reported, would support the view that progressive bulbar palsy, progressive spinal muscular atrophy, and amyotrophic lateral sclerosis are fortuitous variants of a basic disease process.

SUMMARY

The amyotrophic lateral sclerosis symptom complex has been identified in 7 members of a family of Pennsylvania Dutch extraction; 4 generations have been traced.

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Femoral neuropathy

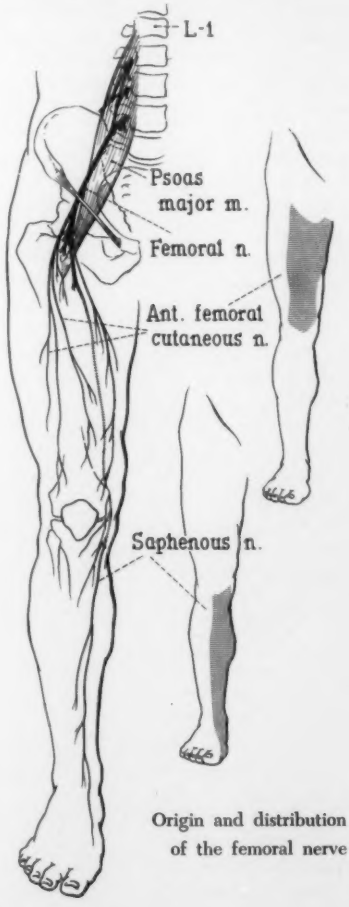
Capt. John R. Calverley, M.C., U.S.A.F., and
Donald W. Mulder, M.D.

INJURY to the femoral nerve or the portions of the lumbar plexus which form this nerve is an important cause of pain, loss of sensation, and weakness in a lower limb. Such neuropathy frequently is a sign of serious systemic disease.

The femoral nerve arises from branches of the second, third, and fourth lumbar nerves, descends through the substance of the psoas muscle, emerges from the pelvis beneath the inguinal ligament, and innervates the sartorius, quadriceps, iliacus, and psoas muscles. It conveys sensation from the anterior and medial surfaces of the thigh and the medial surface of the leg, as shown in the figure. In addition, it contains sensory twigs to the hip joint.

The symptoms of femoral neuropathy include pain and paresthesias in the distribution of the nerve fibers. Muscle weakness makes arising from a chair or climbing stairs difficult. Unless the knee is held in a locked position, it may buckle when walking is attempted. Neurologic examination discloses weakness in flexion of the thigh and extension of the leg. Atrophy of the quadriceps muscle is evident. Sensation in the distribution of the sensory fibers of the nerve may be severely decreased. The quadriceps reflex is usually decreased or absent. It is sometimes difficult to determine whether injury has occurred in the femoral nerve itself or in the fibers of the lumbar plexus which form the nerve.

Abdominal and pelvic operations have been shown to be complicated by injury to the femoral nerve if excessive pressure is brought to bear against the nerve by retractors or if a hematoma is produced within the substance of the psoas muscle during the procedure.[1–5] Winkelman[6] reviewed several cases of femoral neuropathy following parturition. He attributed this lesion to either strong flexion, abduction, and external rotation of the thigh or increased intrapelvic pressure during delivery.



Origin and distribution of the femoral nerve

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Capt. Calverley is on assignment to the Mayo Foundation. The contents of this article are the personal views of the authors and are not to be construed as statement of official Air Force policy nor as Air Force endorsement of any commercial product described.

Bruns[7] in 1890 described 3 patients with mild diabetes who experienced severe hip pain, which was followed by atrophy and weakness of the muscles of the thigh. Garland and Taverner[8] in 1953 reported on older patients with mild diabetes in whom weakness and pain developed in the lower limbs. They attributed this to diabetic myelopathy. Goodman[9] reported that femoral neuropathy is the most common mononeuropathy associated with diabetes. He discussed the data on 17 patients, of whom 15 had pain, 12 had absence of the quadriceps reflex, and 11 had weakness and atrophy of the quadriceps muscle. In his experience, the pain declined soon after the diabetes was brought under control. The paresthesias subsided more slowly, and muscle strength returned in about three months.

Hemophilia was indicated as the cause of a femoral-nerve lesion by Bulloch and Fildes.[10] Their patient was a boy with a disorder of coagulation who manifested a femoral-nerve lesion on one side and, three years later, manifested one on the other side. Since then, several others have reported this complication of bleeding disorders.[11–16] Groch and associates[17] described a patient who received anticoagulant therapy for cerebrovascular disease and, as a complication of this therapy, had a lesion of the lumbosacral plexus. In our experience, bleeding coincident with the administration of anticoagulants may also produce dysfunction of the femoral nerve. Regardless of the nature of the defect in coagulation, the alteration in nerve function is produced by bleeding into the tissues about the nerve or into the nerve sheath itself. Many of these patients have had a mild blow to the inguinal region or have had the onset of their difficulty while bending, lifting, or straining. This was followed by severe pain on hip motion and by a palpable hematoma deep in the lower abdomen. Recovery of strength was nearly complete in three months in some, but there was virtually no recovery after several years in others.

Moffie,[18] in a discussion of 10 patients with evidence of femoral neuropathy, described one with herpes zoster of the sciatic nerve who shortly thereafter had a femoral-nerve lesion; 3 of his patients had severe osteoarthritis of the hip and definite femoral neuropathy for which no other cause could be found. He postulated that the femoral nerve is involved in disease of the hip joint by spread of inflammation from the joint to the psoas muscle and thence to the nerve.

Matthys[19] described 6 patients who sought medical aid only because of femoral neuropathy. In each, the cause for the nerve lesion was an unsuspected disease of another organ; 2 patients had epithelioma of the kidney, 1 had abscess of the kidney, 2 had tuberculous disease of the hip joint, and neuropathy in 1 was attributed to uterine fibroids.

From July 1957 to November 1959, we examined 19 patients whose clinical history and neurologic findings suggested femoral neuropathy. Several types of pathologic processes were found to be responsible for these nerve lesions. Patients with disease illustrative of each of these processes will be described.

REPORT OF CASES

Case 1. A 49-year-old housewife was found to have diabetes mellitus in November 1958, and dietary alterations were suggested. Several weeks later, she had abrupt onset of severe, steady pain in her right hip, the anterior aspect of her right thigh, and the medial portion of her right leg. This pain persisted for several hours. After the pain disappeared, the patient noticed that her right knee buckled when she attempted to walk and that she had a burning sensation in the anterior right thigh when she touched it.

A neurologic examination done four days later disclosed absence of the right quadriceps reflex. Severe weakness of the right iliopsoas muscle and less severe weakness of the right quadriceps muscle were noted. Appreciation of pain and touch was diminished in the distribution of the right saphenous nerve. Vibration was poorly perceived in the toes of both feet. The fasting true blood sugar measured 286 mg. per 100 cc., and the patient was given insulin.

When she was seen again in January 1959, she had no pain but continued to have slight paresthesias over the medial aspect of her right leg. Except for decrease in the right quadriceps reflex and altered appreciation of vibration in the toes, no neurologic abnormalities were found. The fasting blood sugar was 82 mg. per 100 cc.

Case 2. A 52-year-old housewife was told that she had arterial hypertension in 1942. On October 25, 1944, she experienced the abrupt onset of severe, constant pain above her left eye. She was hospitalized and reportedly had no stiffness of the neck. Five days after the onset of pain, she suddenly experienced ptosis and paralysis of the muscles innervated by the left third cranial nerve.

Five weeks after her disability began, she was seen at the Mayo Clinic. She continued to com-

plain of severe pain above the left eye. Her blood pressure was 170/90 Hg. Numerous small hemorrhages and several cotton-wool exudates were seen in each retina. Complete paralysis of the extraocular muscles supplied by the left third cranial nerve was found, as well as ptosis and internal ophthalmoplegia on that side. No other neurologic abnormalities were present. Roentgenograms of the skull did not reveal any abnormalities. The cerebrospinal fluid was clear.

In 1952, the patient was found to have glycosuria. In 1956, she began to take an oral hypoglycemic preparation. In October 1958, she had sudden onset of weakness in the muscles of the right thigh accompanied by a dull, aching pain in the right hip.

Her blood pressure was 175/95. Hemorrhages and exudates were present in the retina, and the retinal arterioles were constricted and sclerotic. The paralysis of the extraocular muscles was unchanged except that the left lid retracted when she attempted to look downward. The right quadriceps reflex was absent, and there was virtually complete paralysis of the right quadriceps muscle. The right iliopsoas muscle was questionably weakened. Sensation was not impaired except in the feet, where vibration was poorly felt. The fasting blood sugar measured 144 mg. The cerebrospinal fluid was clear and contained 80 mg. of protein per 100 cc. No evidence of block of the flow of spinal fluid was discovered. Roentgenograms of the pelvis and lumbar portion of the spinal column showed only hypertrophic changes. Electromyographic needle–electrode study disclosed fibrillation potentials in the right quadriceps and adductor longus muscles.

Case 3. A 50-year-old accountant noticed polyuria and polydypsia in 1955. In June 1957, dull aching pain developed in the lower anterior portion of his right thigh. This gradually increased in severity and spread to involve the entire anterior aspect of the thigh. In October 1957, he was found to have diabetes mellitus.

While the patient was hunting in November 1957, his right knee buckled. Thereafter, he had slight difficulty climbing stairs. In January 1958, burning, tingling paresthesias of both feet developed. When he was examined at the Mayo Clinic in April 1958, the right quadriceps reflex and both gastrocnemius soleus reflexes were reduced. The right quadriceps muscle was weak, and the medial portion of that muscle was slightly atrophic. Sensation was not impaired. The roentgenographic appearance of the lumbar portion of the spinal column was normal. The blood contained 205 mg. of sugar per 100 cc. during a fast, and larger doses of insulin were prescribed.

Case 4. A 67-year-old salesman had a urologic operation in July 1957. He received sulfonamide preparations for control of an infection of the urinary tract. In November 1957, he began to have constant aching pain in the calf of the right leg. Two weeks after the onset of this pain, he became unable to climb stairs easily because of weakness of the muscles of his right thigh. He noticed twitching of these muscles when he was resting. Cells found in the peripheral blood exhibited the lupus erythematosus phenomena, and he was given prednisone by his physician. Early in March 1958, weakness developed in the muscles of the anterior part of the left thigh.

When he was seen at the Mayo Clinic on March 25, 1958, the left quadriceps reflex was absent. The right quadriceps and both gastrocnemius soleus reflexes were reduced. Both quadriceps muscles were weakened and atrophic, particularly the right. Sensation was not altered.

The urine contained a moderate number of leukocytes. The concentration of hemoglobin was 12.7 gm. per 100 cc. of blood. Leukocytes numbered 4,000. The erythrocyte sedimentation rate (Westergren method) was 106 mm. in one hour. The lupus erythematosus clot test gave a negative result. Although the serologic reaction for syphilis had been negative in July 1957, it was positive at the time of this examination. The blood contained 3.8 gm. of albumin, 3.1 gm. of globulin, and 103 gm. of sugar per 100 cc. An electromyogram showed fasciculations in the right extensor digitorum brevis pedis muscle and reduced number of motor unit potentials in the right quadriceps and right anterior tibial muscles.

It was felt that the patient had a mononeuropathy of both femoral nerves and the right peroneal nerve. Muscle biopsy was refused.

Case 5. A 20-year-old construction worker was lifting a very heavy weight when he had abrupt onset of tingling paresthesias over the anterior and lateral aspects of the right thigh. He had no pain and was able to work, but the paresthesias persisted. Three days later, the paresthesias were unchanged. Examination disclosed no evidence of alteration in muscle-stretch reflexes, muscle strength, or sensation. The roentgenographic appearance of the lumbar portion of the spinal column was normal. Five days after their onset, the paresthesias disappeared.

Case 6. A truck driver had severe diarrhea in 1953 when he was 35 years old. His family physician detected a rectal mass which proved to be a grade 1 adenocarcinoma; metastatic lesions were found. In July 1956, the patient had symptoms of intestinal obstruction, and a malignant lesion was found in the ileum. It was not determined whether this was a separate neoplasm or a metastatic one from the tumor previously found.

The patient experienced numbness in the anterior part of the left thigh during November 1957; atrophy was apparent in the same region. Constant pain in the left hip and anterior part of the thigh appeared in March 1958. A myelogram in April 1958 showed no abnormality.

When the patient was examined at the Mayo Clinic in April 1958, the left quadriceps reflex was

absent. The left quadriceps and psoas muscles were severely weakened, and the former was atrophic and exhibited many fasciculations. Appreciation of pain, touch, and temperature was reduced over the anterior part of the thigh on the left. A large, hard mass was palpable in the left inguinal region. It was thought that neither surgical nor roentgen therapy would be of benefit to the patient.

Case 7. A 54-year-old farmer experienced angina pectoris in 1957. During that year, he also began having daily episodes of severe pain of thirty minutes' duration in the right lower abdominal region. He passed 2 to 15 liquid stools daily, which sometimes contained old blood. In April 1958, he had the first of 8 attacks which occurred only when he lifted heavy objects. These consisted of sudden loss of vision, vertigo, diplopia, and dysarthria for two to five minutes. He never had altered consciousness or pain with the attacks.

In June 1958, the patient experienced mild pain in his right hip. Within several days, this pain had spread to the anterior part of the right thigh and knee and had become more severe. Weakness developed in the muscles of his right thigh. On July 18, he noticed vesicular lesions on his right buttock and a tender, right inguinal mass.

He was seen at the Mayo Clinic on July 21, 1958. The muscle-stretch reflexes of the upper and lower limbs were reduced on the right side. The right psoas muscle was slightly weak. Appreciation of thermal sensation was reduced over the medial aspect of the right leg. The firm, tender mass in the right groin proved to be a femoral hernia on surgical exploration. Lesions of herpes zoster were present over the right buttock. Radiographic examination of the colon and stomach did not disclose any abnormalities. Roentgenograms of the lumbar portion of the spinal column showed only hypertrophic ridging. The blood contained 107 mg. of sugar per 100 cc.

A report from the patient in September 1959 indicated that he continued to have pain and weakness in the anterior part of the thigh.

COMMENT

Of our 19 patients with femoral neuropathy, 14 had diabetes mellitus. The historical data on 8 of the 14 patients were remarkably similar. In each, the onset of symptoms of the neuropathy was abrupt and unheralded, with sudden pain in the hip or buttock and the anterior part of the thigh. The pain was associated with weakness, loss of sensation, and alteration of the quadriceps reflex. Symptoms in the remaining diabetic patients developed slowly over several weeks or longer.

The cataclysmic onset in some patients with diabetes suggests that the femoral neuropathy was the result of acute alteration in the blood supply to the femoral nerve. Woltman and Wilder[20] stated that, in practically all cases of diabetic neuropathy, clinical evidence of complicating atherosclerosis was at hand. They felt that the patchy character of the lesions in the nerves and the marked thickening of the walls of the nutrient vessels suggested an ischemic cause for the neuropathy.

Skanse and Gydell[21] reported on a diabetic patient with bilateral femoral-nerve lesions on whom a necropsy report on the femoral nerves was available. Degenerative changes in the myelin sheaths, atrophy of the nerve fibers, and replacement of some of the nerve fibers with fibrous tissue were noted. Thickening in the walls of the vasa nervorum was found.

Dreyfus, Hakim, and Adams[22] discussed the pathogenesis of oculomotor-nerve palsies in diabetics. They described a 60-year-old woman with diabetes who abruptly experienced head pain and oculomotor nerve palsy. At necropsy, the significant lesion was in the involved oculomotor nerve itself. The nerve was considerably swollen in its intracavernous segment. In the swollen part, both the myelin sheaths and the axis cylinders, particularly in the center of the nerve, had disappeared. Considerable atherosclerosis of the large cerebral vessels was found. All the vessels within the nerve were narrowed but not entirely occluded. The nerve palsy was likely the result of decreased blood supply to the nerve. The similarity between the onset of the nerve lesion in this patient and the onset of the femoral neuropathy in some of our patients is apparent. Our patient 2 also had had sudden onset of head pain and oculomotor palsy thirteen years before femoral neuropathy developed. In addition to their femoral nerve lesions, many of the 14 patients with diabetes had the symptoms and neurologic findings of a more typical diabetic peripheral neuropathy. They complained of burning of the feet and had altered appreciation of vibration, touch, and other types of sensation in the feet. Involvement of the femoral nerve was an isolated event that could readily be distinguished from the more distal neuropathy.

None of the patients included in this study had severe back pain or pain that suggested irritation of a lumbar nerve root. Electromyography and myelography were carried out in

many of the patients, and in none was a lumbar nerve root or intraspinal lesion evident.

Subsequent reports available from 5 of our patients with diabetes disclosed that, in 4 of them, recovery or improvement of the femoral neuropathy occurred in one to six months.

Patient 4 had lesions of several peripheral nerves, including both femoral nerves. It was felt that his mononeuropathy multiplex was the result of polyarteritis nodosa, with associated impaired blood supply to involved nerves.

We can only speculate whether patient 5 damaged his femoral nerve by overstretching the nerve itself or by damaging the nutrient vessels by stretching them. Another of our patients, a diabetic, experienced marked worsening of symptoms while he was lifting.

Retroperitoneal tumors, especially lymphomas, have been alleged to be a frequent cause of femoral neuropathy.[23] In our series of patients, only one had definite evidence of involvement of the femoral nerve by tumor.

The etiology of the femoral neuropathy in patient 7 is not entirely clear. He had herpes zoster in the distribution of the sciatic nerve, atherosclerosis, and a femoral hernia. Any of these factors could conceivably have been responsible for his femoral-nerve lesion.

A patient with the symptoms and neurologic findings of femoral neuropathy declined additional diagnostic procedures.

Patients with obviously advanced malignant disease or hematomas associated with bleeding disorders are not often seen by a neurologist; thus, it is likely that the true incidence of femoral neuropathy from these causes is higher than we have reported here. It is possible that variations in the method of use of certain types of surgical retractors have prevented femoral-nerve damage during the operations performed in the period covered by this study. We have not seen femoral neuropathy after parturition.

SUMMARY

Neuropathy of the femoral nerve may cause severe pain, weakness, and loss of sensation. Such neuropathy previously has been reported in association with diabetes mellitus, hemophilia, abdominal malignant disease, and hip-joint disease and as a complication of operations on the abdomen and pelvis.

Of 19 patients with femoral neuropathy in this series, 14 had diabetes mellitus. It is postulated that, in at least some of these diabetics, neuropathy developed as a result of acute alteration in the blood supply to the femoral nerve. In 3 patients, the femoral neuropathy was related to polyarteritis nodosa with decreased blood supply to the nerve, lifting heavy weights with abduction of the thighs causing traction on the nerve, and metastatic disease directly involving the nerve. In 2 patients, the cause was not discovered.

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Vertebral artery compression in cervical spondylosis

Arteriographic demonstration during life of vertebral artery insufficiency due to rotation and extension of the neck

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IN THE PAST DECADE, cervical spondylosis has been recognized as a cause of previously obscure neurologic syndromes.[5-9,22,35,36,48] In the excellent clinical and pathologic studies cited, direct compression of cervical nerve roots and spinal cord by osteophytes, degenerated disks, and displaced vertebrae has been emphasized as the most common cause of signs and symptoms.

For the past two years, our attention has been focused on patients with cervical spondylosis complaining of neurologic symptoms that appeared to be of a vascular nature because they were often transient and involved regions of the nervous system above and rarely below the cervical area and because attacks were precipitated in a predictable manner by hyperextension and rotation of the neck. Typical symptoms in such patients include vertigo, hearing loss, monoparesis, hemiparesis, quadriparesis, ataxia, and a special type of postural collapse without loss of consciousness which we believed to be pathognomonic for the condition (the "drop attack"). Rarely, there are complaints of paresthesias in the upper thoracic dermatomes, presumably due to interference with the blood supply of the anterior spinal artery. From experience with cases of vertebral-basilar artery insufficiency due to atherosclerosis,[26,30,31,32,47] it seemed likely, on clinical grounds, that such symptoms might be due to episodic ischemia of the brain stem, inner ear, and upper thoracic spinal cord resulting from vertebral-artery compression by osteophytes, which is known to occur in cervical spondylosis.[2,7,15,20,21,25,35,36,39,40,41,48,50,51] It also seemed likely that compression of the vertebral arteries, should it prove to be present, was more severe during rotation and extension of the neck. The most common site of formation of osteophytes is at the uncinate portion of the vertebrae (Figs. 1 and 2). This is the junction of the centrum and lateral masses in development of the vertebrae and is also known as the neurocentral joint, Luschka's joint, and the uncovertebral joint. There is disagreement on whether this is a "true" joint or not.[4,15,36]

The brain stem, inner ear, and upper thoracic cord lie within the territory of supply of the vertebral arteries and their branches (basilar, internal auditory, and anterior spinal arteries). Little doubt exists that the cervical cord and its roots may also be rendered ischemic, but, since direct compression occurs at these sites, this possibility is difficult to prove. Necropsy studies by Hutchinson and Yates[20,21] have shown that spondylosis with vertebral artery compression commonly occurs in association with atherosclerosis of major cerebral vessels, and it is evident that, if the two conditions occur together, the liability to ischemic episodes is increased. Important necropsy studies by Tissington, Tatlow, and Bammer[50]

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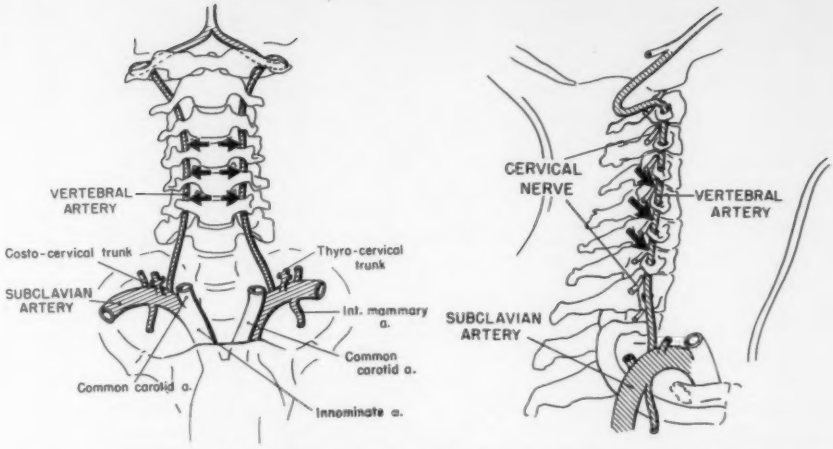

Fig. 1. Anteroposterior and lateral views of vertebral artery to show anatomic divisions and sites of compression. Part 1 is portion between subclavian artery and sixth cervical vertebra. Part 2 is course of vessel through transverse foramina. Part 3 is course around atlas. Part 4 is terminal part as it enters foramen magnum to join its partner and form basilar artery. Arrows indicate most common sites of compression of vertebral artery by osteophytes.

and de Kleyn and Nieuwenhuyse[11,12] showed that hyperextension and rotation of the neck of the cadaver compressed the contralateral (to the face) vertebral artery at the atlas and axis. In one cadaver with spondylosis, illustrated by Tissington, Tatlow, and Bammer, there was significant worsening of the compression of the ipsilateral vertebral artery by an osteophyte during rotation of the neck. Virtamo and Kivalo[54] demonstrated in cadavers the marked alteration in the vertebral arteries by osteophytes, especially with the head turned to the opposite side.

In order to investigate a large series of living patients with symptoms presumed to be due to spondylotic vertebral artery compression, we have developed a simple percutaneous method of performing transbrachial vertebral angiography similar to the method developed independently and recently reported by Pygott and Hutton.[40]

The development of this arteriographic technic and subsequent demonstration of vertebral artery compression by osteophytes in the neck have enabled us to define the syndrome of vertebral artery compression due to cervical spondylosis. We now believe this syndrome to be common. We have also studied a large

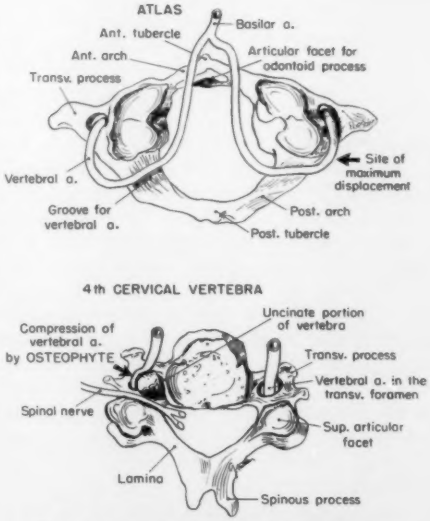

Fig. 2. Anatomic relation of vertebral artery to vertebrae. Vertebral artery lies alongside uncinate portion of vertebra, most common site of degenerative changes due to cervical spondylosis with osteophyte formation. Vertebral artery also lies immediately anterior to emerging cervical nerve root and intervertebral foramina.

number of patients presenting with symptoms of vertebral-basilar arterial insufficiency,[29–32] which occasionally may be confused with carotid artery insufficiency,[31] in whom we did not suspect cervical spondylosis on clinical grounds but who proved at angiography to have compression of the vertebral artery by exostoses. With increasing experience, we have now come to recognize the syndrome of vertebral-basilar artery insufficiency due to a combination of cerebrovascular atherosclerosis and cervical spondylosis.

The purpose of this communication is to summarize the arteriographic findings in a total of 46 patients with recurrent cerebrovascular symptoms and/or spondylosis and to present and discuss in detail 26 illustrative cases of the syndrome of vertebral-basilar artery insufficiency due to cervical spondylosis which were selected from the group of 46 cases. After discussion of the mechanisms involved in the production of symptoms, possible approaches to medical and surgical therapy will be considered.

MATERIAL AND METHODS

Clinical case material. A group of 26 patients in whom cervical spondylosis with vertebral artery compression was proved to be present by arteriography was selected. All patients were examined by one or more of the authors at the Detroit Receiving Hospital. After careful clinical history, complete neurologic examination, lumbar puncture, and cervical spine roentgenograms, both vertebral and both carotid arteries were studied angiographically;* 26 patients with symptoms proved to be due to cervical spondylosis were selected from the total of 46 with cerebrovascular symptoms or spondylosis. A single case in which only 1 severely compressed vertebral artery was visualized by arteriography has been included, although no attempt was made to visualize the opposite vertebral artery.

Arteriographic technics used. All arteriograms were performed under local anesthesia because we believe general anesthesia (with its hazards of hypotension) is contraindicated in the arteriographic evaluation of cerebrovascular disease. Injection of the carotid artery was made by percutaneous puncture with an 18-gauge needle inserted into the common carotid artery below the bifurcation; 8 to 10 cc. of Renografin or Hypaque was injected with a 10-cc. syringe.

Vertebral artery injection was made by 2 methods. The first 34 of the 46 patients examined were studied by retrograde subclavian vertebral angiography (using percutaneous puncture of the subclavian artery above the clavicle) in a manner similar to that described by Barbieri and Verdecchia,[2] Crawford, DeBakey, and Fields,[10] and Meyer, Sheehan, and Bauer[31] using the technic of Shimidzu.[46]

After some time, we became dissatisfied with percutaneous puncture of the subclavian artery for the following reasons:

1. Technical difficulty in maintaining the needle in the vessel due to movement of the patient with occasional extravasation of dye. The needle was therefore continuously held by the examiner with consequent liability to radiation exposure.

2. Possible injury to the brachial plexus (1 case), and possible traumatic pneumothorax (no cases)

3. Supraclavicular insertion of a needle is an unpleasant experience for the patient.

Because of this, we developed a percutaneous method that obviated all of the objections listed above. This technic has now been used successfully in 40 cases, including the 12 cases presented here, and will be described in detail.

Percutaneous transbrachial vertebral arteriography is now performed under local anesthesia after premedication with Seconal and Demerol. A Stille-Werner cannula-needle (Ohio Chemical and Surgical Equipment Co., Madison, Wis.), equivalent to gauge 17 for a size PE 160 polyethylene catheter, is inserted percutaneously into the brachial artery in the antecubital fossa. A polyethylene catheter is then inserted by the method described by Seldinger, who used this technic for femoral arterial catheterization.[40,45,55] Its advantage is that a catheter larger than the needle can be used.[45] A metal catheter guide is inserted through the cannula, which is then removed over the guide. A polyethylene catheter (size

*This is part of a collaborative study of extracranial causes of cerebrovascular disease sponsored by the National Heart Institute of the U. S. Public Health Service, under the chairmanship of Dr. Michael E. DeBakey.

PE 160 or PE 205) 14 in. or more in length is then placed in the vessel over the metal guide and advanced to the desired site (near the origin of the vertebral artery from the subclavian artery or, occasionally, into the aortic arch to exclude an anomalous origin of the vertebral artery). This can be estimated on each patient by approximate measurement externally. The metal guide is then removed, leaving the catheter in place, and injections are made. We use syringe injection either by hand or by a mechanical injector (Keith Pressure Injection Device, Toronto) with compressed oxygen from a tank as the propelling force. The mechanical injector permits injection of a relatively large bolus of dye through a small size catheter. We have used solutions of 30 or 60% Renografin (diatrizoate methylglucamine) or 50% Hypaque (diatrizoate without methylglucamine) as contrast solutions, and, since the 50 or 60% solutions proved to be most satisfactory, these concentrations are now used routinely.

Both vertebral arteries and the basilar artery and its branches can be adequately visualized by 7 injections; 15 cc. is injected on right and left sides with roentgenogram projections in the anteroposterior projection to visualize the arteries in the neck, and 20 cc. is injected on right and left sides with the head rotated to the right and left side to provide a lateral view of the extra- and intracranial vessels. Thus, each vertebral artery is visualized with the head straight, to the left, and to the right. Finally, a single 20-cc. injection is made, with a Towne projection, to visualize the basilar artery and its branches in the anteroposterior view of the skull. Thus, a total of 130 cc. of dye is used in 7 divided doses to study in detail the entire subclavian-vertebral basilar system and any changes brought about by rotation of the neck. Since the catheter is in the subclavian artery and not in the vertebral artery, only a small portion of the injected dye enters the cerebral circulation. An additional 40 cc. of dye is used to visualize the carotid arteries. This is routinely carried out before injection of the vertebral-basilar system. We have used as much as 210 cc. of radiopaque material in the same patient on the same day without ill effects, and we now consider vertebral arteriography by this new percutaneous brachial technic to be less objectionable to the patient than carotid arteriography. Furthermore, the procedure is not time-consuming.

Arteriographic complications. There have been 4 complications of all types of arteriography in the present series of 26 cases reported here in detail. None was fatal or permanent.

Case 8. A woman, age 59, had thrombophlebitis from an infection at the site of puncture of her left arm after brachial catheterization. She recovered promptly with antibiotic treatment.

Case 10. A man, age 67 had 3 brief focal seizures involving the right limbs after injection of the left carotid artery. He had no residual neurologic deficit.

Case 25. A man, age 52, suffered injury to the left brachial plexus from the needle during percutaneous puncture of the subclavian artery in the supraclavicular fossa. Over the subsequent six months, the left biceps and deltoid muscles slowly regained normal strength. This complication was one of the reasons why the percutaneous brachial technic was developed.

Case 26. A man, age 53, had transient right homonymous hemianopsia and confusion following left vertebral artery injection after catheterization via the brachial artery. All abnormal neurologic signs cleared within two days. Possible causes may have been hypotension, which occurred in this patient, clotting in the catheter, which is unlikely because we use continuous saline irrigation, or an unusual reaction to the dye.

It should be emphasized that there are two important differences between the percutaneous brachial technic described above and that described earlier by Radner[41] and, later, Hauge[18] and Olsson.[34] First, Radner exposed the radial artery in the forearm by means of a surgical incision, with subsequent ligation, whereas, in the method described here, the catheter is inserted percutaneously into the brachial artery at the antecubital fossa, by the technic of Seldinger,[45] and the vessel is spared ligation. Second, Radner advised inserting the catheter directly into the second portion of the vertebral artery to obtain optimum visualization of the cerebral branches by the less satisfactory contrast media then available. This is potentially hazardous with atherosclerosis of the vertebral arteries because it may displace mural thrombi. The purpose of the technic described here is to visualize the entire course of the vertebral-basilar system, including the origin of the vertebral artery from the sub-

clavian artery as well as the intracranial portion of the basilar artery.

The vertebral arteries have been studied by means of a catheter inserted in the femoral artery and passed in a manner retrograde to the subclavian artery.[28,37] Other investigators at the present time are visualizing the vertebral-basilar system by retrograde injection of the brachial artery after incision and operative exposure under general anesthesia and placing a cannula through the vessel wall. The advantage of the technic described here is that it can be performed by simple percutaneous puncture without surgery, general anesthesia, blood loss, or sacrifice of the brachial artery. All these are important considerations in aged and atherosclerotic individuals. In brief, in our hands, this technic has become a simple and safe medical procedure. It should be emphasized that direct puncture of the second portion of the vertebral artery is contraindicated in cerebrovascular disease because [1] puncture of a diseased and atherosclerotic vessel may cause thrombosis or embolism, [2] the origin of the vessel, which is not visualized, is commonly the site of atherosclerotic plaques, [3] the vessel may be developmentally small or absent, and [4] effects of rotation of the head cannot be studied.

Normal vertebral arteriogram. Before any description can be made of the abnormal vertebral arteriograms, there are several points with regard to the normal arteriographic appearance of the vertebral artery which should be emphasized. The vertebral artery is the first branch of the subclavian artery, arising from the superior and posterior wall of the vessel. It is customarily divided into 4 parts (Fig. 1), and this terminology will be used throughout this paper.

Part 1. After arising from the subclavian artery, the vessel passes upward and backward to enter the transverse foramina of the sixth cervical vertebral.

Part 2. The artery has a straight course encased in the bony canal formed by the transverse foramina (Fig. 2) of the upper 6 cervical vertebrae.

Part 3. After emerging from the transverse foramina of the atlas, the artery runs horizontally posteriorly and medially around the articular processes of the atlas, lying in a groove on the upper surface of the posterior arch of the atlas (Fig. 2).

Part 4. Finally, the artery passes anterior to the oblique ligament of the atlas and enters the vertebral canal. It pierces the spinal dura and passes upward into the posterior fossa through the foramen magnum, where it unites with the other vertebral artery to form the basilar artery (Fig. 2).

Important branches of the subclavian artery that are located in the vicinity of origin from the vertebral artery include [1] the internal mammary, which arises opposite the vertebral artery and passes downward into the thorax, and [2] the thyrocervical trunk, which gives rise to the ascending cervical and inferior thyroid branches as well as the suprascapular and superficial cervical branches.

If the above two vessels are filled by the contrast media and the vertebral artery is not, one can be certain that the dye was injected in proper position and quantity and that, presumably, the vertebral artery is absent or occluded or possibly has an anomalous origin from the aorta or common carotid arteries.

The other branches of the vertebral artery will not be mentioned here except for the spinal branches, which arise from the medial side of the second portion of the artery, pass through the intervertebral foramen, enter the vertebral canal, and give off twigs to the roots of the spinal nerves which anastomose with the anterior and posterior spinal arteries. These branches may become impinged upon by osteophytes in cervical spondylosis and cause additional ischemic cord damage.[9,31] From the point of view of vascular disease, an important anatomic consideration is the potential anastomoses of branches of the vertebral artery with other vessels of the head and neck. The third part of the vertebral artery anastomoses with the descending branch of the occipital artery and with the deep branches of the cervical artery (Fig. 3) after occlusion of the first or second part and provides collateral circulation, as suspected by us previously.[31] The artery in its fourth part is known to have a few branches that pierce the dura and anastomose with the meningeal branches of the occipital artery, the ascending pharyngeal arteries, and, occasionally, branches of the middle meningeal artery. If compression, steno-

sis, or occlusion of the vertebral artery is slow in development, these vessels may increase in size sufficiently to provide a collateral circulation distal to the site of obstruction.

The abnormal vertebral arteriogram. *Spondylotic compression.* Arteriographic abnormalities in the vertebral-basilar system in the total group of 46 patients with symptoms due to cerebrovascular disease or spondylosis are summarized in Table 1. They are listed in detail because the vertebral arteries, being encased in bone, are difficult to expose by dissection and rarely have been examined at necropsy. Vertebral artery displacement by osteophytes was found in 26 cases. Specific listing of all roentgenographic abnormalities noted in the spondylosis group will be found with the clinical summaries in Table 2. Occasionally, mention has been made in technical reports concerned with vertebral angiography of compression or displacement of this vessel by exostoses,[18,40,41] but, as far as we are aware, no extensive or detailed clinicoangiographic study of spondylotic compression of the vertebral arteries has been reported previously. After review of the vertebral angiograms in the 26 patients in whom spondylosis was confirmed by roentgenographic examination of the cervical spine with accompanying compression of the vertebral arteries, certain features are considered to be characteristic of this condition. The vertebral artery in severe cervical spondylosis has a strikingly tortuous ("washboard") appearance, with multiple sigmoid curves, the lateral concavities of which lie opposite an intervertebral space. Stenosis is frequent and occlusion rare at the point of maximal concavity. Close inspection of the anteroposterior or oblique films usually permits identification of the compressing osteophyte attached to the uncinate portion of the vertebra (Fig. 2) which compresses and displaces the artery at each point of curvature or narrowing (Figs. 4, 5A, 6A and 8 through 11).

The most common sites of vertebral artery displacement are between the fifth and sixth and the fourth and fifth cervical vertebrae. Less commonly, there is displacement between the third and fourth vertebrae, and rarely does it occur between the second and third. Displacement of the first part of the artery between its origin from the subclavian artery and its entry into the transverse foramen of the sixth vertebra is not uncommon, but this displacement is more often secondary to arteriosclerosis than to osteophytes.

Fig. 3. *(Case 17)* Left carotid arteriogram. Left vertebral artery is occluded in Parts 1 and 2 of its course (Fig. 5), and a collateral circulation is provided by anastomoses between Part 3 of vertebral artery and descending branch of posterior occipital and deep cervical arteries.

Comparison of films taken before and after rotation of the neck shows that severe stenosis of the vertebral artery due to compression by osteophytes may be converted into complete obstruction by this maneuver (Case 7, Fig. 4) or the stenosis may become more severe (Case 12, Fig. 8). Sometimes, the maneuver during arteriography was accompanied by symptoms of dizziness, blurred vision, and confusion (Case 19, Fig. 9A; Case 11, Fig. 11). Since compression of the vertebral artery may reduce the head of pressure distally, the posterior cerebral arteries and, occasionally, the upper end of the vertebral-basilar system become filled by dye during carotid arteriography. This retrograde filling of the basilar artery and its branches has been reported in 2 cases of vertebral artery occlusion by Van der Swan.[53] Compression of the vertebral arteries by osteophytes may increase on the

TABLE 1

ARTERIOGRAPHY OF ALL 4 MAJOR CEREBRAL VESSELS IN 46 SUBJECTS WITH CEREBROVASCULAR SYMPTOMS OR CERVICAL SPONDYLOSIS

Abnormality of arteriogram	*Number of Subjects*
Atherosclerosis of basilar artery and branches	22
Atherosclerosis of carotid artery and branches	29
Compression or displacement of vertebral arteries by osteophytes	26
Right vertebral artery	26
Left vertebral artery	16
Cervical spondylosis by routine spine films	34
Vertebral artery narrowing (congenital or acquired)	13
Right vertebral artery	6
Left vertebral artery	7
Occlusion or absence of vertebral artery	4
Right vertebral artery	0
Left vertebral artery	4
Normal vertebral arteries	7
Atherosclerotic tortuosity of vertebral arteries (independent or osteophytes)	10
Stenosis of origin of vertebral artery from subclavian	6
Right vertebral artery	1
Left vertebral artery	4
Both vertebral arteries	1
Aneurysm of right carotid bifurcation (asymptomatic)	1

side opposite to which the head is turned by stretching; however, compression is more severe on the same side due to pressure against the osteophytes.

It is important to differentiate (as far as is possible in arteriograms) between changes due to external pressure by osteophytes and those due to intrinsic causes such as arteriosclerotic tortuosity and atherosclerotic plaques (Fig. 6). Since the 2 diseases are commonly associated, this is not always possible. However, from a functional point of view, the 2 procedures have similar effects—a reduction in arterial flow. The functional importance of certain postures of the neck which tend to embarrass vertebral arterial circulation will be discussed later. An additional 8 patients had cervical spondylosis demonstrated by roentgenograms of the spine but no associated compression or displacement of the vertebral arteries. Of these 8, 3 had one vertebral artery significantly more narrow than the other.

Other abnormalities. Of the 46 patients admitted to hospital with complaints referable to cerebrovascular disease and spondylosis, 22 were found to have abnormalities of the basilar artery and/or its branches. These abnormalities included stenosis, plaques, tortuosity, and elongation with dilation or obstruction of one or more branches. Likewise, 29 patients had similar changes in the extra- and intracranial portion of the carotid arteries and/or its branches. In the entire series, atherosclerotic involvement was commonly widespread and often proved a deterrent to attempts at corrective surgery. An unsuspected saccular aneurysm was found in a patient who had never had evidence of intracranial bleeding.

It was of particular interest that only 7 patients out of the total 46 were found to have what we considered to be arteriographically normal vertebral arteries. Significant vertebral artery narrowing was found in 13 (this did not include those with moderate narrowing, which was common); all of these patients had 1 artery that measured one-third or less of the

TABLE 2

CLINICAL TABLE AND ARTERIOGRAPHIC FINDINGS IN 26 CASES OF VERTEBRAL ARTERY COMPRESSION BY SPONDYLOSIS

Case number	*Age*	*Race*	*Sex*	*Blood pressure*	*Duration of symptoms*	*Clinical summary*	*Radiographic findings*
1	55	W	M	126/70	49 months	Superior homonymous hemianopsia at onset. Dizziness, dysarthria now	Cervical spondylosis. Occlusion right posterior cerebral. Tortuous right vertebral artery at osteophytes
2	56	N	F	120/86	14 months	Dizziness, ataxia, postural syncope, cerebellar signs, paresthesias in fingers and toes	Elongated, dilated basilar artery. Aneurysm right internal carotid (asymptomatic). Small left vertebral artery. Tortuous right vertebral with spondylosis
3	68	N	F	140/70	19 months	Dizzy spells on rotating neck. Transient quadriplegia, collapse without loss of consciousness (drop attack). Paresthesias of hands and feet. Cerebellar signs. Bilateral Babinsky signs. Hearing loss bilaterally. Diabetes	Plaque left anterior cerebral artery. Basilar dilated and elongated. Plaques intracranial portion right vertebral. Left and right vertebral tortuous and compressed by osteophytes. Cervical spondylosis
4	59	W	M	155/100	9 years	Left hemiparesis 9 years, episode akinetic mutism 7 years ago. Spasticity. Muscle wasting hands. Cerebellar signs. Bilateral weakness. All DTR's increased. Bilateral Babinski signs. Paresis lateral gaze	Basilar elongated and dilated. Atherosclerosis internal carotid arteries in the skull. Occlusion left vertebral at origin. Right vertebral tortuous due to osteophytes. Cervical spondylosis, severe
5	59	W	F	150/85	40 months	Vertigo, tinnitus, syncope, headache many drop attacks. Ataxic	Left carotid in neck tortuous and "kinked" on itself. Right vertebral tortuous. Cervical spondylosis
6	74	W	M	140/80	2 years	Dizzy, sees "red flares" before syncope. Ataxic. Cerebellar signs. Vertical nystagmus. Bilateral hearing loss. Hypalgesia both legs	Narrowing left carotid due to atherosclerosis. Left vertebral smaller than right. Plaques right carotid in neck. Both vertebrals tortuous due to cervical spondylosis. Plaques left subclavian artery
7	63	N	M	170/120	24 months	Right hemiparesis 2 years before admission. Later had dizziness, blurred vision, confusion. Broad based ataxic gait, cerebellar tremor. EEG: slow waves left side. Died	Occlusion left carotid in neck (bifurcation). Bilateral cerebral filling from right carotid. Both vertebrals tortuous due to severe cervical spondylosis
8	59	N	F	190/120	1 year	Nausea, emesis, ataxia, confusion, weakness both legs. Paresis left lateral gaze. Left facial weakness. Nystagmus. Dysphagia. Right Babinski sign. Phlebitis left arm after transbrachial arteriogram	Multiple plaques both carotids in neck and skull. Very small and tortuous left vertebral. Narrow basilar artery. Right vertebral tortuous and narrowed due to severe cervical spondylosis. Plaques left subclavian artery.
9	55	W	M	140/78	3 years	Left hemiparesis 3 years. Subsequent paresthesias, blurred vision, vertigo upon arising. Parkinson facies, tremor, bilateral spasticity, incoordination. Ambulatory. Diabetes	Atherosclerosis carotid arteries. Basilar elongated and tortuous. Right vertebral tortuous and narrowed. Left vertebral dilated and tortuous. Cervical spondylosis
10	67	N	M	210/110	19 months	Diplopia, ataxia, emesis, headache. Paresis lateral gaze, ptosis. Vertical and horizontal nystagmus. Cerebellar signs. Ataxic gait. Focal seizures after left carotid arteriogram	Nonfilling right anterior cerebral. "Kink" left vertebral at C4, with narrowing tortuous right vertebral. Basilar elongated and dilated, cervical spondylosis, severe
11	43	N	M	114/76	5 years	Dizziness with head turned to left, pain left side of neck, arm, and chest wall. Admitted with pain, vertical and horizontal nystagmus, left fifth hypalgesia, weakness left arm and leg, decreased left biceps reflex	Severe cervical spondylosis. Lateral displacement both vertebrals with head straight and marked compression both vertebrals with head turned to same side as artery studied

(Continued on following page)

TABLE 2—*(continued)*

Case number	*Age*	*Race*	*Sex*	*Blood pressure*	*Duration of symptoms*	*Clinical summary*	*Radiographic findings*
12	48	W	M	120/80	2 months	Drop attack, blurred vision, dizziness, transient blindness. Dizzy if he turns his head quickly. Pain in neck. Blacksmith	Carotids dilated and tortuous. Both vertebrals tortuous due to severe spondylosis. Plaque in left vertebral
13	63	W	F	114/70	23 months	Dysphagia, dysarthria, blurred vision, vertigo after surgery, with quadriparesis and nystagmus. Now transient dizziness, ataxia, blurred vision	Stenosis basilar artery. Occlusion proximal portion left vertebral, tortuous right vertebral, spondylosis
14	68	N	F	240/110	10 years	Tinnitus, scotomas, vertigo, paresthesias right leg and arm, transient blindness 10 years ago. Mild right side paresis. Bilateral extensor plantars	Stenosis left anterior cerebral. Basilar elevated and tortuous. Both vertebrals tortuous due to severe spondylosis
15	58	N	M	180/120	7 years	Vertigo, ataxia, transient blindness, syncope, paresthesias right side. Right facial weakness and hemiparesis. Cerebellar signs. Died of hypertensive hemorrhage	Both carotids dilated, tortuous. Right vertebral small, tortuous. Left vertebral tortuous due to severe cervical spondylosis
16	61	N	F	110/80	9 months	Emesis, weakness, diplopia, blurred vision, ataxia; vertical and horizontal nystagmus. Bilateral plantar extensors	Tortuous carotids in neck and skull. Elongated tortuous basilar. Both vertebrals tortuous due to cervical spondylosis
17	52	N	M	170/110	40 months	Transient weakness right face, arm with aphasia and rapid clearing 1956. Recent hearing loss, dysarthria, tinnitus, blurred vision	Stenosis left carotid (cavernous portion). Occlusion right middle cerebral. Minute left vertebral, tortuous right vertebral due to spondylosis. Left vertebral fills in cranium via anastomosis with left posterior occipital artery
18	49	N	M	124/70	13 months	Neck pain, vertigo and transient blindness with rotation of neck. CNS lues	Marked tortuosity of carotid arteries. Both vertebral arteries displaced by spondylosis
19	51	W	M	100/60	11 years	Drop attack age 40. Progressive spastic paraplegia since. Diplopia. Paresthesias in fingers and toes. Nystagmus. Hyperactive reflexes. Laminectomy done, no block present	Carotids normal. Right vertebral arteries tortuous due to spondylosis, severe. Left vertebral not studied
20	73	W	M	190/110	10 years	Syncope, ataxia, gets dizzy when he looks to the ceiling. Nystagmus. Cerebellar signs. Mild weakness right arm. Drop attacks	Plaques both carotids. Dilated, tortuous basilar artery. Vertebrals tortuous. Right vertebral displaced by bony spur. Severe cervical spondylosis
21	56	W	F	130/92	3 years	Vertigo, episodic dysphagia, tinnitus, gaze paralysis, nystagmus, spasticity, ataxia	Basilar elongated and dilated. Carotids normal. Tortuous vertebral arteries due to cervical spondylosis
22	59	W	M	180/90	19 months	Apraxia of gait, episodic blindness. Poor phonation. Rigidity right arm. Pseudobulbar speech	Occlusion left anterior cerebral artery. Stenosis right anterior cerebral. Stenosis origin. Left vertebral with plaque more distal. Tortuous right vertebral. Basilar elongated and dilated. Cervical spondylosis
23	64	N	M	110/76	7 months	Headaches, dizziness, left homonymous hemianopsia, sudden onset blindness. Peripheral left seventh palsy. Paresis of gaze. Cerebellar signs. Ataxic	Carotids: Plaque right neck. Right vertebral tortuous due to cervical spondylosis. Left vertebral very small
24	61	W	M	140/70	2 years	Weakness, headache, numbness of his hands, ataxia. Cerebellar signs	Carotids normal. Basilar stenosis. Both vertebrals tortuous. Cervical spondylosis, severe
25	52	N	M	140/80	14 months	Dizziness, ataxia, upon arising. Nystagmus. Left brachial neuritis after subclavian arteriography	Carotids normal. Tortuous right vertebral. Cervical spondylosis
26	53	N	M	150/85	3 years	Vertigo, emesis, ataxia, tinnitus, nystagmus, blurred vision 3 years. Left hemiparesis 1 year. Cerebellar signs. Transient confusion and right hemianopsia after left vertebral arteriogram	Carotids normal. Both vertebrals tortuous due to cervical spondylosis

diameter of its larger partner and presumably would provide an insufficient supply of blood to the basilar artery should the larger artery become occluded, either temporarily or permanently. In 2 instances, the narrowed vertebral artery had an internal diameter of between 1 and 2 mm., and it is doubtful that the blood flow was of significance (Figs. 4 and 5). Similar findings were reported in the anatomic dissections reported by Stopford.[49]

In 4 cases, 1 vertebral artery was occluded (or absent), all on the left side. It is often difficult to be certain whether nonfilling is due to occlusion of the vessel or to congenital absence or anomalous origin of the vessel unless the area is explored surgically. If there is filling of a small "stump" by radiographic material at the usual site of origin of the vertebral artery (as occurred in 2 cases with associated widespread vascular disease), one can be reasonably certain that the artery has become occluded rather than being congenitally absent.

Stenosis at the origin of the vertebral artery from the subclavian artery, presumably due to plaque formation, was found in 6 patients. In 3 of these, large atheromatous plaques were evident in the subclavian artery near the origin of the vertebral artery; 5 had stenosis of the left vertebral artery. Tortuous and dilated vertebral arteries due to diffuse arteriosclerosis independent of any tortuosity caused by exostoses (Fig. 6B) were noted in 10 patients. The 2 sites of this arteriosclerotic type of tortuosity are [1] the origin of the subclavian artery before it enters the transverse foramen at C6 and [2] the point at which the artery leaves the transverse foramen of the atlas to pass over the posterior aspect of the atlas. At the latter site, the artery may become so elongated and tortuous that it may become acutely flexed or "kinked" and obstruct itself during extension and rotation of the neck to the same or opposite side (Fig. 6B).

Clinical considerations in spondylotic compression of the vertebral arteries. The 26 patients with spondylotic compression of the vertebral arteries demonstrated radiographically ranged in age from 43 to 74 years. These cases are summarized in Table 2. The earliest age at which symptoms referable to compres-

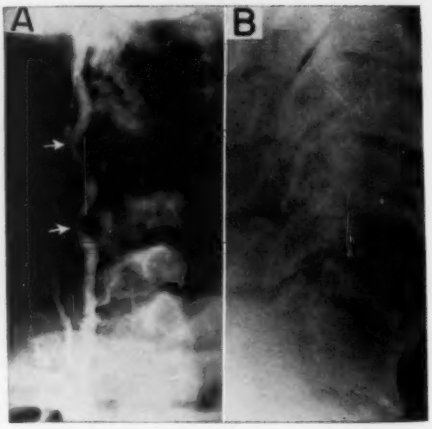

Fig. 4. *(Case 7)* [A] Second part of vertebral artery showing marked displacement and compression by osteophytes of cervical spondylosis, most marked at areas indicated by arrows. Maximum internal diameter measures 4 mm., at arrow 2 mm. On rotation of head to left, column of dye became obstructed at lower arrow. [B] Lateral view of cervical spine showing severe spondylosis

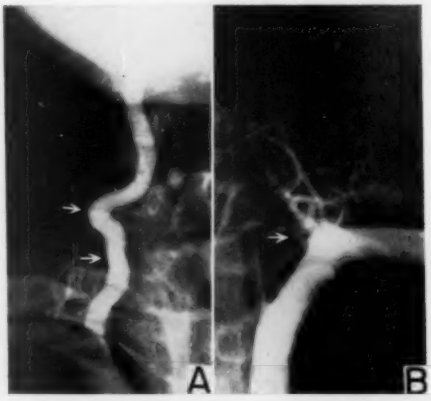

Fig. 5. [A] Wide vertebral artery on right compressed and displaced by cervical spondylosis at C6-7. [B] Arrow indicates occluded vertebral artery on left, measuring 2 mm. in internal diameter. Same subject seen in Figure 3. It is possible that small vessel shown to left of arrow may be a rudimentary or atretic vertebral artery, although we believe it is a cervical branch. From a functional point, there is no significant blood channel in usual site of vertebral artery.

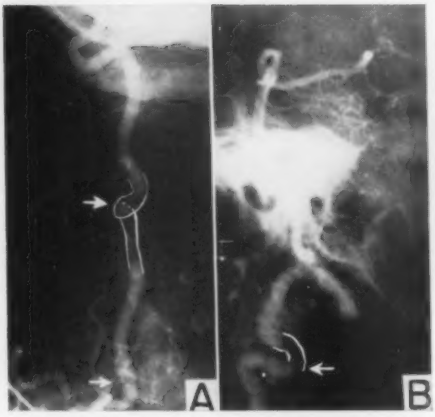

Fig. 6. [A] Displacement and kinking of second part of vertebral artery on right due to spondylosis and arteriosclerosis indicated by arrow. [B] Left vertebral artery shows arteriosclerotic tortuosity independent of spondylotic displacement.

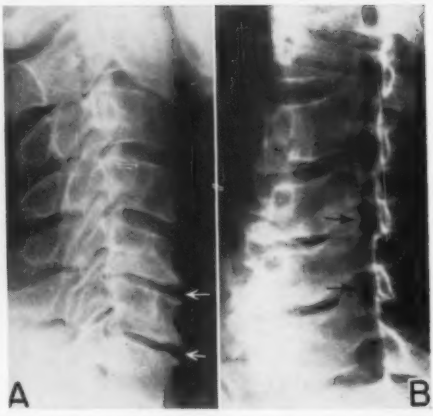

Fig. 7. [A] Lateral views of cervical spine *(Case 12)* to show marked spondylosis with "lipping" and narrowed disk spaces. [B] Oblique view to show encroachment of intervertebral foramina (black arrows) by osteophytes

sion of the vertebral arteries by cervical spondylosis occurred was 38 years by history. (However, we have recently examined another patient with compression proved by arteriography whose symptoms were present at age 32 years.) Of the 26 patients, 11 were hypertensive and 3 were diabetic; 12 were Caucasian, and 14 were Negro. Since approximately 60% of admissions to the Neurology Service of the Receiving Hospital are Negroes, we do not consider any significant difference in racial incidence to be present. Of the patients, 18 were male and 8 female, which we believe to be a significantly greater frequency in the male (possibly related to greater predisposition to neck trauma in the male).

The duration of symptoms varied from two months to eleven years, with a mean duration of approximately two years; 12 patients have had symptoms for three years or longer, and 2 patients have died during the two years that this survey has been in progress. The clinical and arteriographic data in the entire series are summarized in Table 2.

The most common complaint was dizziness and/or vertigo, present in 18 of the 26 cases; this was frequently the presenting complaint. Many of the patients volunteered that they had difficulty in walking straight, and some complained that they were occasionally accused of being "drunk." Presenting complaints in 5 subjects were transient dizziness or blurred vission when they turned to look over their shoulder or looked upward at the ceiling; 18 patients complained of transient ataxia or were found to be ataxic on examination. Of the total group of 26, only 3 did not complain of dizziness, ataxia, or both; 14 patients noted episodic visual disturbances consisting of blurred vision on turning the head, sometimes associated with scotomas or, rarely, temporary blindness. Headache was common.

Of special interest was the complaint by 6 patients of the "drop attack," by which is meant a sudden transient quadriparesis resulting in falling to the ground without loss of consciousness. This will be discussed in detail below.

Symptoms referable to head posture were noted by 5 patients; they became "dizzy" (faint, light-headed, or vertiginous) when they rotated the head to the extreme lateral position or hyperextended the neck, and, in 1 other patient, rotation of the head during a radiologic procedure produced the complaint of "dizziness." Illustrative case summaries will be

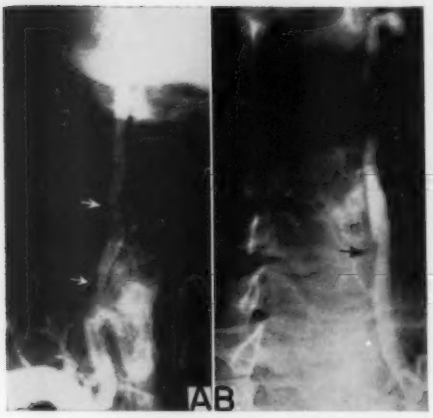

Fig. 8. *(Case 12)* [A] Arrows indicate compression of vertebral artery by osteophytes with reduction of internal diameter from 6.5 to 4 mm. at points of narrowing. [B] Left vertebral artery. Stenosing lesion indicated by arrow is only visible on rotation of neck.

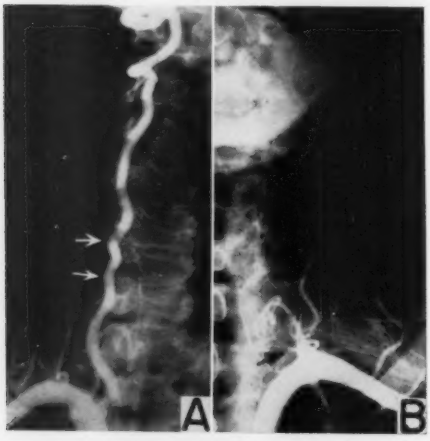

Fig. 9. [A] Right percutaneous transbrachial vertebral arteriogram in Case 19, a 51-year-old man suffering from severe cervical spondylosis with an eleven-year history of drop attacks followed by spastic paraplegia on extension and rotation of head. During arteriography, rotation of head to left produced symptoms of dizziness and confusion. Internal diameter is reduced from 5 to 1 mm. at points of narrowing (shown by arrow). [B] Right percutaneous transbrachial arteriogram in Case 15, a 58-year-old hypertensive woman with a seven-year history of vertigo, ataxia, blindness, syncope, and right-sided weakness and parasthesias with cerebellar signs. Arrows indicate displacement and angulation of right vertebral artery by cervical spondylosis. Right common carotid artery, brachiocephalic trunk, and subclavian artery are also visualized.

Fig. 10. *(at left)* [A] Severe cervical spondylosis with displacement by osteophytes (upper arrows) and proximal stenosis (lower black arrow). [B] Arrow indicates total occlusion of left vertebral artery with short stump proximal to site of occlusion.

presented below; for the sake of brevity, only relevant details of the neurologic examination and laboratory studies will be given.

Case 3. On several occasions during a period of nineteen months before admission, a 68-year-old diabetic woman had noted that, if she looked sharply to either side, she would momentarily become dizzy. The final attack of dizziness terminated in abrupt collapse to the ground without loss of consciousness. She lay there unable to move any of her extremities and was brought to the Emergency Room of the Receiving Hospital, where quadriplegia was noted. She was conscious, fully oriented, and able to speak normally. Shortly after admission to hospital, she recovered sufficiently to be able to walk but was ataxic for several days. Wasting was present in the left biceps and small muscles of the left hand; the left triceps and brachioradialis reflexes were de-

Fig. 11. Retrograde transbrachial vertebral arteriograms in a 43-year-old man with cervical spondylosis and intermittent symptoms of cerebral ischemia of five years' duration associated with rotation of neck. [A] Left vertebral angiogram with head rotated to left; arrows indicate vertebral artery compression by osteophytes (C3-C6). [B] Minimal displacement without compression when head turned to right. [C] Right vertebral arteriogram showing minimal displacement without compression with head turned to left. [D] Marked compression with head turned to right

pressed, but all tendon jerks were increased in the lower extremities and both plantar reflexes showed extensor responses. Muscle weakness of both upper extremities with cerebellar signs was also noted. A clinical diagnosis of cervical spondylosis with vertebral artery compression was made, and roentgenograms of the cervical spine confirmed the presence of marked spondylosis. Arteriograms were interpreted as showing an atheromatous plaque in the left anterior cerebral artery, an elongated and dilated basilar artery, and atheromatous plaques in the intracranial portion of the right vertebral artery. Both vertebral arteries were compressed and stenosed by exostoses in the second portions.

Comment. With the advanced cerebrovascular atherosclerosis present, it is evident that cerebrovascular insufficiency could be precipitated by turning the head to either side.[3] This maneuver stretches the vertebral artery on the opposite side and compresses the vessel against exostoses on the same side, reducing vertebral blood flow to the point of ischemia of the lower brain stem and eventually resulting in a "drop attack" with quadriplegia (probably due to ischemia in the region of the pyramidal decussation).

Case 12. A 48-year-old blacksmith entered the hospital because of dizziness, collapse, and blurring of vision. His occupation is significant because, while shoeing horses, he placed his head and neck against the flank of the horse, resisting any movements of the animal with his head. This occupation presumably was responsible for the severe cervical spondylosis shown to be present radiographically (Figs. 7 and 8). One week before admission, he "collapsed" on arising from his bed in the morning and everything went "dark;" he did not lose consciousness and eventually was able to get up from the floor and return to bed, where he rested as much as possible before entering hospital. During the period of bedrest at home, he noted on several occasions that, when he hyperextended his neck or turned his head to either side, he would become dizzy and his vision would become blurred. Examination after admission to hospital showed tenderness on palpation of the muscles of the neck with limitation of motion. Neurologic examination was otherwise within normal limits. Arteriographic examination showed both vertebral arteries to be tortuous and displaced by exostoses (Fig. 8), with the probable formation of an atherosclerotic plaque at the site of displacement and compression on the left (Fig. 8B). Rotation of the head to the opposite side during arteriography reduced the caliber of the vessel from 6 to 4 mm. Both carotid arteries were

dilated and tortuous but were neither stenosed nor obstructed.

Electroencephalographic studies were performed with this patient sitting on a chair. The routine electroencephalogram with and without hyperventilation was normal. An electrocardiogram was recorded with the electroencephalogram,[50] and records were made while the carotid arteries in the neck were alternately massaged and compressed for five seconds. No change occurred in the electroencephalogram or electrocardiogram, nor were any symptoms produced. The neck was then hyperextended and the head rotated to either side. This maneuver consistently produced dizziness, vertigo, and blurring of vision within 10 to 20 seconds without change in the electrocardiogram or electroencephalogram. A combination of rotation of the head, carotid compression, and tilting to 70° in such patients has been shown to produce electroencephalographic change, although each maneuver alone may be ineffectual.[51]

Case 19. A man, aged 51, suffered several drop attacks beginning at the age of 40; in the ensuing years, he had chronic progressive spastic paraplegia and, four years before admission, became bedridden. The first drop attack occurred while he was reaching and looking upward to close overhead garage doors, at which time he suddenly collapsed to the ground. He got up to walk to the house and suddenly collapsed again; he was assisted indoors, where he rapidly recovered. He did not lose consciousness during either of these two attacks. During arteriography, it was noted that he became dizzy and confused whenever his head was turned sharply to the left for the lateral projections, before any dye was injected. Only the right vertebral artery was injected, but, during rotation of the head to the left, severe compression and stenosis by osteophytes were demonstrated, the artery being reduced in caliber from 5 to 1 mm. during rotation (Fig. 9A).

Case 20. A man, aged 73, with a history of severe hypertension, suffered a drop attack ten years before admission. He stood up suddenly from the sitting position, extended his neck, and collapsed without loss of consciousness. He got to his feet, was noted to "stagger around," and had to hold on to the furniture when walking. He recovered completely but, shortly before referral to hospital, collapsed while walking on the street. He did not lose consciousness and remembers falling to the sidewalk and being helped to another hospital, where a scalp laceration was treated. When referred to the Detroit Receiving Hospital, he volunteered the information that, whenever he looked upward, he would become dizzy. This was confirmed on physical examination by hyperextension of the neck. Roentgenograms revealed severe cervical spondylosis; arteriograms showed atherosclerotic plaques in both carotid arteries and dilation and tortuosity of the basilar artery with tortuosity of both vertebral arteries, which were displaced by osteophytes. Atherosclerotic stenosis at the origin of the left vertebral artery was also noted.

Case 11. A male engineer and construction worker aged 43 years was admitted because of radiating pain in the left arm and left chest aggravated by coughing on flexion or rotation of the neck. He complained of dizziness on stooping, with staggering, and became dizzy when he turned his head left. He was a wrestler in high school and college and was 37 when he had his first attack of dizziness and tinnitus. On 2 occasions, he had suffered from syncope, once preceded by photopsia.

Significant physical findings were tenderness over the fifth cervical vertebra, vertical and lateral nystagmus, hypalgesia of the left face, and weakness of the left arm and leg. Terminal tremor was present in the left hand, and vibratory and position sense was decreased on the left side of the body. He was treated with halter traction.

Cerebrospinal fluid dynamics were normal (without block), but the total protein was 67 mg. per cent. Roentgenograms of the cervical spine showed old compression deformities of C5 and C6, narrowing of disk spaces, anterior spurring, and an old avulsion fracture of an anterior spur of C5. Absence of the normal lordotic curve and irregular narrowing of the intervertebral foramina of C4, 5, and 6 were noted.

Bilateral carotid arteriograms showed no significant abnormalities. However, the left posterior cerebral artery filled very well during left carotid artery injection. Bilateral transbrachial vertebral arteriograms were done. When the head was turned to the left during this procedure, he complained of being uncomfortable and dizzy and "thought he would black out."

The left vertebral artery without rotation of the head measured 4 mm. in diameter with minimal displacement between C4-5 and C5-6. With the head turned to the left, significant compression was seen at 3 levels. At C3-4 and C4-5, the lumen was reduced to 3 mm.; at C5-6, the lumen was reduced to a diameter of 2 mm. With the head turned to the right, no significant changes in the second portion of the vertebral artery were noted (Fig. 11).

The right vertebral artery without rotation of the head measured 5 mm. in diameter. With the head turned to the right, the vertebral artery was reduced at C3-4 and C4-5 to a diameter of 4 mm. and, at C5-6, the lumen measured 2.5 mm. With the head turned to the left, no significant arteriographic change other than mild lateral displacement was seen.

It is apparent from the clinical and arteriographic descriptions of the above 5 cases that symptoms referable to ischemia of the vertebral-basilar system were provoked by hyperextension or rotation of the neck. In all, marked cervical spondylosis was present with displacement and/or compression of the vertebral ar-

teries, and, in all, there was some radiographic evidence of atherosclerosis or arteriosclerosis of the other cerebral vessels (Table 2). In 3 patients, it was apparent during arteriography that rotation of the neck produced worsening of the compression of the vertebral arteries with consequent further narrowing. In 2 patients, the demonstrable narrowing of the vertebral artery on rotation of the neck was accompanied by symptoms (Case 19, Fig. 9A; Case 11, Fig. 11).

DISCUSSION

Semeiology of vertebral artery compression by osteophytes. It is not the purpose of this paper to discuss signs and symptoms due to direct compression of nerve roots and spinal cord in cervical spondylosis. The pathologic changes and their pathogenesis due to osteophytic compression are now well established.[5–9,15,25,35,36,48] Kovacs[22] has reported vertebral artery compression due to subluxation and deformation of the cervical apophyseal joints. Many of our patients had symptoms and signs referable to such compression of cervical cord and roots; for example, in Case 3, the wasting and weakness of the hands with depressed tendon jerks and spasticity of the lower extremities are believed to be due to direct compression of the spinal cord and nerve roots by osteophytes. The purpose of this communication is to stress the frequent occurrence of symptoms and signs due to compression of the vertebral artery in the neck in cervical spondylosis and to point out that these symptoms may occur in the absence of compression of cervical roots or cord. The symptoms and signs of spondylotic compression of the vertebral artery are episodic and are characterized by their reversibility in early stages; at this stage, they are amenable to treatment, although repeated attacks tend to culminate in progressive irreversible damage to the brain stem. The symptoms and signs of this disease tend to be precipitated by hyperextension and rotation of the neck (looking upward, turning the head to look over the shoulder), and these maneuvers may be used intentionally by the physician as a diagnostic test or inadvertently during certain procedures (rotation of the head during roentgenography or hyperextension of the neck during intubation for anesthesia). Vertebral artery compression by osteophytes is frequently accompanied by cerebral atherosclerosis of other vessels, which predisposes the individual to attacks because the collateral circulation is reduced. Congenital absence or smallness of one vertebral artery (noted in several of our patients) will also predispose the individual to attacks when the opposite vessel is compressed by exostoses.

It is possible that repeated traumatic injury of the vertebral artery by spondylotic exostoses may predispose the vessel to the formation of atherosclerotic plaques. This possibility was discussed by Hutchinson and Yates,[20,21] and we are inclined to believe that this is likely for several reasons: [1] some arteriographic defects occurring in relation to spondylotic exostoses appear to have superimposed plaques (Fig. 9B, Case 12); [2] cervical spondylosis and cerebrovascular atherosclerosis both occur in the same age groups; [3] damage to large vessels with other diseases (syphilis, giant-cell arteritis, hypertension) predisposes the injured area to atherosclerosis; [4] the usual sites of atherosclerosis of the vertebral artery are at its origin from the subclavian artery and in Parts 3 and 4, but involvement of Part 2 by atherosclerotic plaques is rare, except in association with spondylosis.[10,13,20,21,40]

A glance at Tables 1 and 2 will show that there are distinctive features in the semeiology of vertebral artery compression due to cervical spondylosis. The disease is more common in the male (18:8), whereas symptoms due to vertebral-basilar artery atherosclerosis alone show no comparable sex difference.[29] Since our series of patients was derived entirely from the laboring class, sex difference in this series may be related to the more frequent occurrence of occupational injury to the neck in the male. In Case 12, for example, there can be little doubt that repeated trauma to the neck played a part in the production of symptoms. The mean age at which symptoms became prominent in this series of patients was 57, but the ages of our patients ranged from 43 to 74 years. Hypertension was present in 11 cases and diabetes mellitus in several others. It is believed that the latter factors contribute indirectly to the production of symptoms by increasing the incidence of atherosclerosis.[29]

The drop attack was suffered by 6 patients who described episodes in which they suddenly collapsed, usually after hyperextension or rotation of the head. When asked closely about these attacks (which we consider pathognomonic of vertebral-basilar artery insufficiency due to vertebral artery compression), the history was elicited that "the legs suddenly gave way," "my legs collapsed," "my legs were paralyzed," or "I couldn't move a muscle from the neck down." Consciousness was not lost, but, after collapsing to the ground, they found themselves momentarily helpless and usually had a rapid recovery from the tetraplegia or tetraparesis over the ensuing one to fifteen minutes.

A man aged 59, Case 4, had a typical attack while driving a car (glancing to one side?). A woman aged 59, Case 5, described numerous drop attacks always occurring when she crossed a street (looking to either side for advancing traffic?). In this series and in other patients with cervical spondylosis examined by us, permanent brain stem damage has resulted from hyperextension of the neck. A male patient had severe pontine hemiplegia after endotracheal intubation with hyperextension of the neck. A woman had ataxic quadriparesis after carrying a high stack of firewood, partly supported under her chin, with her neck hyperextended.

Numerous other reports have been made of brain stem infarction, ischemia, and vertebral-basilar artery thrombosis occurring in normal individuals after chiropractic manipulation of the neck and fracture-dislocation of the cervical spine, particularly the odontoid process.[1,11,12,14,17,22–24,27,38,42–44] All authors are agreed that, in displacement of the cervical vertebrae, compression of the vertebral artery may result in such catastrophes, and postmortem studies[11,12,50] have shown that rotation of the head to one side results in narrowing of the vertebral artery on the opposite side, particularly where it is normally angulated as it winds around the atlas. It has also been shown in cadavers with incidental cervical spondylosis that rotation of the neck increased compression of Part 2 of the vertebral artery by osteophytes.[50,54] We have made similar observations in living subjects with cervical spondylosis and have demonstrated that:

- The syndrome of spondylotic vertebral artery compression is characterized by symptoms of vertebral-basilar artery insufficiency and can be diagnosed clinically and subsequently confirmed by angiography.
- Rotation and hyperextension of the neck may be used to produce symptoms comparable to those of which the patient complains.
- Symptoms produced by rotation and hyperextension of the neck are caused by increased compression of Part 2 of the vertebral artery with stenosis or occlusion at the sites of exostoses (Figs. 4A, 9A, and 11). This compression or occlusion by osteophytes during rotation of the neck is in addition to the physiologic narrowing of Part 3 of the vertebral artery which occurs in all individuals during rotation of the head.
- Stenosis and occlusion of other major cerebral vessels due to atherosclerosis or developmental anomalies predispose the subject to symptoms due to spondylotic vertebral compression.

The term "drop attack" was first suggested by Kremer,[23,24] who has given an excellent clinical description of this symptom occurring in cases of injury in the region of the cervical spine or due to medullary compression, with reference to the work of Hammond, Merton, and Sutton.[19] We assume it is due to sudden ischemia of the pyramids in the region of the decussation, which are ventrally placed in the medulla and lower brain stem and are supplied by the terminal branches of the vertebral arteries (including the anterior spinal arteries and first part of the basilar artery). The term has all the advantages required for common usage; it is brief, simple, and descriptive. It emphasizes the sudden collapse of posture (drop) due to paralysis of the lower limbs; it also implies reversibility and absence of loss of consciousness (attack). The drop attack must be differentiated from epilepsy, syncope, and Stokes-Adams attacks. In reviewing some of the earlier case reports of cervical spondylosis, symptoms suggestive of the drop attack are occasionally mentioned, although they were apparently not recognized as such, and given such names as "akinetic epilepsy." In view of the association of very severe cervical spondylosis with syringomyelia and syringobulbia,[8] one wonders if the rare, mysterious, and epi-

TABLE 3

SEMEIOLOGY OF SPONDYLOTIC COMPRESSION OF THE VERTEBRAL ARTERIES

Symptoms

Dizziness, vertigo, blurred vision, ataxia, drop attacks (usually on rotation or extension of neck), headache

Signs

Due to vertebral artery compression
Bilateral or unilateral spasticity, cerebellar signs, nystagmus, visual field disturbances, gaze palsy, internuclear ophthalmoplegia, fifth, seventh, eighth, ninth, tenth, and twelfth nerve weakness, hemisensory loss
Due to nerve root compression (need not be present)
Wasting of upper extremities, fasciculation, loss of tendon jerks, segmental sensory loss in upper extremities and trunk (T4)

Tests

Symptoms usually produced by rotation or hyperextension of neck (dizziness, blurred vision, confusion, nystagmus). Carotid compression test negative except when neck rotated or extended

Electroencephalogram

Normal with hyperventilation and during symptoms after rotation of head. Carotid compression usually produces no electroencephalographic or electrocardiographic change until head is rotated.

Cervical spine roentgenograms

Cervical spondylosis

Carotid arteriograms

Commonly associated arterio- or atherosclerosis. Posterior cerebral arteries and occasionally basilar artery fill (low pressure in vertebral-basilar system)

Vertebral arteriograms

Marked displacement and/or compression by osteophytes, more marked on rotation of head

Treatment

Bed rest, limitation of neck movement, anticoagulant drugs, ? surgical immobilization of the neck or decompression of transverse foramina

sodic attacks of collapse seen in that condition (usually ascribed to extension of the syrinx into the brain stem) may, indeed, be drop attacks of the same etiology as those described here.

Relation to carotid sinus sensitivity. It was considered possible that rotation and hyperextension of the neck might produce symptoms by carotid sinus sensitivity with consequent cardioinhibitory and vasodepressor reflexes. That this mechanism did not occur was demonstrated by provoking the symptoms by rotation of the head while electroencephalograms and electrocardiograms were recorded and by testing for carotid sinus sensitivity with carotid sinus massage and stimulation. No sinus reflex bradycardia was noted to occur during rotation of the head with the production of symptoms (2 cases), nor was there any fall in blood pressure with this maneuver (1 case).

Similar results in evaluating cases with symptoms during rotation of the neck were briefly mentioned by Gastaut, Vigouroux, and Dell[16] in an extensive study of carotid sinus sensitivity, but these authors made no mention of vertebral artery compression. However, a few clinically similar cases, unproved by arteriography, were reported by Toole[51] in his detailed electroencephalographic and polygraphic study. In brief, he found that electroencephalographic changes did not appear in a group of subjects who complained of cerebrovascular symptoms on extension or rotation of the neck nor when the carotid artery was compressed without rotation of the head, but, when the head was rotated with the carotid artery still compressed, electroencephalographic slowing did appear. This suggests itself as a simple electroencephalographic test (which we are presently evaluating) for testing patency or insufficiency of the vertebral artery, that is, by compression of the carotid artery before, during, and after rotation of the head to one side. Slowing appearing only when the head is rotated to one side implies that the opposite vertebral artery is carrying a critical supply of blood which becomes reduced by compression when the neck is rotated.

The clinical observation that transient symptoms such as syncope, nystagmus, vertigo, and drop attacks may be precipitated by rotation of the head has been noted previously by others,[4,11,12,16,23,24,31,42,43,50,52] but, in the large series presented here, the pathogenesis has been demonstrated during life, permitting classification of the semeiology, diagnosis, and

treatment of the syndrome of "spondylotic vertebral artery compression" (Table 3).

TREATMENT

Medical. It has been our practice to place patients on complete bedrest for three weeks during the acute episodes and to instruct them to avoid hyperextension and rotation of the head as much as possible. In severe cases, we have prescribed a light-weight plastic neck collar that prevents excessive movement of the neck.

In those patients with severe ischemia of the brain stem or occipital lobes, we have used heparin and Dicumarol therapy with good results similar to those reported by others.[23] It is our belief that, when severe compression and stenosis of the vertebral artery occur, deposits of mural thrombus may result with possible fragmentation and embolism to distal vessels. We believe empirically that this is prevented or minimized by anticoagulant therapy. That such thrombosis does occur is evident from necropsy studies in fatal cases.[15,27] In general, the results of this regimen have been satisfactory, although the follow-up of our cases has not exceeded two years. It is our clinical impression that the disease may have a more benign course than vertebral-basilar atherosclerosis, the recovery from attacks being more prompt and fatal outcome and severe disability being less common. However, it should be emphasized that not only does the disease mimic atherosclerosis of the vertebral-basilar artery with insufficiency but the two diseases also are commonly associated.

Surgical treatment. Only one of our patients has undergone surgical treatment, but two possible therapeutic approaches come to mind: [1] fixation of the neck to limit motion and [2] decompression of the transverse foramina. In both methods of treatment, there is the danger of surgical trauma to the diseased vessel with resultant thrombosis, as well as trauma to the cervical nerve, which lies adjacent to the vertebral artery.

SUMMARY

A disease entity which we propose to term "spondylotic vertebral artery compression" is described. A group of 26 cases has been collected in which the diagnosis was confirmed by arteriography. A simple percutaneous technic in which the vertebral artery is injected with diatrizoate after catheterization of the brachial artery under local anesthesia is described. The disease occurs most commonly in the sixth decade and is characterized by symptoms of vertebral-basilar arterial insufficiency commonly precipitated (by history) or provoked (at the bedside) by rotation or hyperextension of the neck. Additional signs and symptoms of compression of cervical nerve roots and/or cervical spinal cord due to the cervical spondylosis may or may not be present. Associated atherosclerosis or arteriosclerosis of cerebral vessels is commonly present and predisposes the individual to symptoms. A pathognomonic sign of the disease is the "drop attack" in which the patient collapses (usually after rotation of the neck) without loss of consciousness. The disease is more common in males than in females. Illustrative cases are described with illustrations of accompanying changes in the cervical spine and vertebral arteries demonstrated by angiography. The pathogenesis, diagnosis, and treatment of this condition are discussed.

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Effects on the brain of extracorporeal circulation in open heart surgery

A neurologic, electroencephalographic, psychometric, and neuropathologic study

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MORE CONCERN has been expressed over the vulnerability of the brain than perhaps of any other organ in patients undergoing cardiac surgery with extracorporeal circulation. This communication describes the incidence of cerebral complications in 24 consecutive patients operated upon with the help of cardiopulmonary bypass at the Mount Sinai Hospital during 1958. This incidence was established by detailed clinical neurologic, electroencephalographic, and psychologic examinations before and after surgery. Neuropathologic study was performed in most of those patients who did not survive surgery.

MATERIALS AND METHODS

The ages of the 24 patients ranged from 3 to 51 years, almost half being under 10. The cardiac lesions operated upon included interatrial and interventricular septal defects, tetralogies of Fallot, aortic stenosis, mitral insufficiency, and myxoma of the right atrium. Preoperative neurologic examinations were performed in all patients the day before surgery. A routine 8-channel, 13-lead electroencephalogram was obtained within the week preceding operation in 17 patients. Full scale Wechsler-Bellevue intelligence and Bender-Gestalt figure tests were administered preoperatively to 11 patients. The Wechsler intelligence scale for children was utilized when necessary.

The premedication employed before surgery consisted of meperidine, scopolamine, and promethazine. Thiopental sodium or cyclopropane was used for induction, and light anesthesia was maintained during surgery with endotracheal nitrous oxide–oxygen. Succinylcholine aided in the control of respiration. Cardiopulmonary bypass was established by means of the DeWall bubble oxygenator. Total perfusion times ranged from thirteen to 162 minutes but were generally less than thirty minutes. Elective cardiac arrest was induced by acetylcholine or potassium in 8 patients. A 2- or 3-channel Medcraft electroencephalogram was obtained from all patients during surgery; 4 electrodes were employed, 2 over each hemisphere.

Detailed postoperative neurologic examinations were performed the night of surgery on all patients who survived. Only unequivocal and persistent findings were considered as valid. Electroencephalographic and psychologic studies were repeated as soon as the patient was ambulatory and could tolerate such testing. This usually occurred one to two weeks after surgery. The criteria for electroencephalographic abnormality at this hospital have been stated elsewhere.[1] Postmortem examination was made of the brains of 8 patients who died. Special investigations for gas[2,3] or antifoam[4] emboli were not performed.

RESULTS

Neurologic examination. Preoperative neurologic abnormalities were observed in only 1 patient, a 3½-year-old child with the tetrad of Fallot who was markedly retarded and walked with an abnormally broad-based gait.

Postoperative examinations were performed on 16 patients, 8 others having died during or

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shortly after surgery. Although varying degrees of recovery of alertness after perfusion were noted, new unequivocal neurologic findings were observed in 3 patients. The first was a 51-year-old man who had undergone surgery for calcific aortic stenosis. After he had reacted from anesthesia, he suddenly began to have right-sided, and then generalized, seizures, became semicomatose, and had a right hemiparesis. The second patient was a 7-year-old child operated upon for an interatrial septal defect. She had left focal seizures shortly after surgery and showed ptosis of the left eyelid and bilateral extensor plantar responses. The third patient was a 10-year-old boy operated upon for congenital aortic stenosis. He was examined postoperatively during a period of respiratory distress and was found to have dissociated eye movements and a right plantar extensor sign and to be markedly obtunded. Both the respiratory distress and the neurologic findings in this patient improved after bronchoscopy and adequate bronchial aspiration.

Electroencephalography. All but 1 of the 17 preoperative electroencephalograms were normal. The abnormal record came from a 13-year-old girl with an interatrial septal defect and consisted of diffuse, symmetric, 3- to 4-cps burst activity. Postoperative tracings were obtained in 11 patients; 2 of these records, which were normal before surgery, became abnormal. Both showed reduction from their basic alpha frequencies and symmetric, diffuse or temporal bursts of 1½- to 3-cps activity. Neither of these patients had abnormal neurologic findings. The 10-year-old child with abnormal neurologic findings during a period of postoperative hypoxia also had an abnormal postoperative record (diffuse 3- to 6-cps bursts). Unfortunately, a preoperative electroencephalogram was not obtained.

The electroencephalographic changes observed during surgery were similar to those described by other workers.[5–10] These changes characteristically occur during certain distinct periods: at the time of placement of the superior vena caval catheter; at onset of perfusion; during prolonged perfusion; and immediately after perfusion. Those changes attendent upon caval catheterization resulted from difficulty with catheter placement or reduction of the functional lumen of the cava. With the onset of perfusion, correction or progression of these abnormalities were observed. In those instances in which minimal changes appeared before perfusion, the alteration would appear at the onset of perfusion. Almost all of the 24 patients showed some slowing at the onset of perfusion. Adjustment of catheter position or flow rate usually was sufficient to correct the abnormality. Perfusions that lasted more than thirty minutes tended to be associated with progressive slowing of the record.

Asymmetric slowing during perfusion was noted in 2 patients. These patients also experienced postoperative focal seizures and had neurologic abnormalities. The record of the 51-year-old man with postoperative right focal and general seizures and right hemiparesis was flat on the left side for almost eight minutes. A large amount of 1½- to 3-cps activity was also present on the left for some time, with much less abnormality on the right. The 7-year-old girl with postoperative left focal seizures showed 1- to 2-cps activity on the right for thirty seconds. Unfortunately, both of these patients died before full 8-channel postoperative electroencephalograms could be obtained.

Asymmetry of the electroencephalogram during perfusion may therefore be a significant occurrence. Similar significance could not be placed on other types of abnormalities. Thus, a normal postoperative electroencephalogram and normal examination were obtained in a patient whose tracing during perfusion was isoelectric for periods up to twenty seconds. Symmetric records as slow as 1½ cps for fifty seconds were also obtained in patients who had normal postoperative neurologic examinations. However, more prolonged electroencephalographic abnormalities were generally associated with a poor prognosis.

Psychologic examination. Postoperative psychometric studies were performed in 7 patients. Of these, 6 received higher scores in the postoperative Wechsler-Bellevue test and 1 did slightly worse; 3 patients did significantly better on the performance scale, while 1 showed improvement in the verbal scale. These changes may be due to practice effect or the relative lack of postoperative anxiety and are probably not significant.

Table 1. Summary of Patients with Definite Cerebral Involvement

Patient	Age	Cardiac diagnosis	Result of surgery	Significant preoperative conditions	Complications during surgery	Duration of perfusion	Induce cardiac arrest	Electroencephalogram during perfusion (maximal) abnormality)	Postoperative neurologic examination	Postoperative electroencephalogram	Percentage change in Wechsler-Bellevue	Postmortem examination of brain
G. L. *	51	Acquired calcific aortic stenosis	Died second day	Angina; 2 previous myocardial infarcts	Hypotension; ? new coronary	52 minutes	18 minutes	Flat on left for over 8 minutes; diminished voltage on left thereafter; 1 to 3 cps for over 20 minutes, left much more than right	Right-sided and generalized seizures; right hemiparesis; semicomatose			Mild "anoxic" changes in cortex
J. R.	7	Interatrial septal defect	Died first day	None	Hypofibrinogenemia	20 minutes	Not used	1 to 2 cps for 30 seconds on right; symmetric 3 to 5 cps for over 2 minutes	Left-sided seizures; ptosis on left; bilateral Babinski Signs			Ecchymosis on cerebrum, cerebellum; hemorrhage in corpus callosum
L. R.*	10	Aortic stenosis	Survived	None	Transient auricular fibrillation	28 minutes	17 minutes	Symmetric slowing; 1½ cps for 70 seconds	Very drowsy; disconjugate eye movements; right Babinski	3- to 6-cps bursts diffuse	Improvement compared to school IQ scores	
G. P.	5	Tetrad	Died after few hours	Episodic cyanosis; syncope	Transient hypotension	60 minutes	35 minutes	Symmetric slowing; flat for 30 seconds; 1½ cps for 3 minutes				Marked congestion; perivascular edema of white matter
R. F.†	12	Supravalvular aortic stenosis	Died during surgery	Angina	Aortic insufficiency	101 minutes	49 minutes	Progressive symmetric slowing up to time of death				"Anoxic" changes in cortex
J. S.	41	Acquired aortic stenosis	Died during surgery	Syncope; ? previous cerebral episode	Arterial catheter slipped	29 minutes	Not used	Symmetric slowing; almost flat 40 seconds; 1 to 3 cps for 80 seconds				"Anoxic" changes in cortex
C. R.	7	Interatrial septal defect	Survived	None	None	23 minutes	Not used	Symmetric slowing; 1½ cps for 40 seconds on several occasions	Normal	2½ -cps bursts, left more than right; α=8-10 (preoperative: α=9-10)	†7.1%	
M. I.	14	Interatrial septal defect	Survived	None	Supraventricular tachycardia	13 minutes	Not used	Symmetric slowing; 1 to 2 cps for 20 seconds	Normal	1.5- to 3-cps bursts; 4- to 6-cps diffuse; α=7-9 (preoperative: α=8-10)	Not done	

*Preoperative electroencephalogram not obtained. All other patients in this table had normal preoperative electroencephalograms, and all had normal preoperative neurologic examinations.
†This patient has been reported in detail elsewhere.[11]

No changes in the quality of figures or numbers of recalled figures were found in the Bender-Gestalt test.

No correlation was found between the results of these tests and the neurologic and electroencephalographic examinations. A patient with an abnormal electroencephalogram postoperatively showed improvement in his Wechsler-Bellevue test score. The 10-year-old boy who had abnormal neurologic findings and an abnormal electroencephalogram postoperatively was tested only after surgery. The results, when compared with the intelligence scores obtained from his school, showed improvement.

Neuropathology. Of the 8 brains subjected to gross and histologic study, 5 were abnormal. Changes compatible with anoxia were found in 3 brains. These changes, which were limited to the cerebral cortex, included pycnotic nuclei, eosinophilic swollen cytoplasm, and a decrease in the number of neurons. (These changes are listed as compatible with anoxia due to their lack of specificity.) Loss of Purkinje cells was observed in 1 cerebellum. The brain of the 51-year-old man with the postoperative seizures and right hemiparesis showed these changes.

Ecchymoses were found on the cerebrum and cerebellum of the brain of the 7-year-old girl who experienced left focal seizures and had other neurologic findings postoperatively. Sectioning revealed a hemorrhage in the corpus callosum. Hypofibrinogenemia had developed during extracorporeal circulation, and there were clinical and pathologic evidences of hemorrhage elsewhere in her body.

The remaining abnormal brain was that of a 5-year-old child who died suddenly a few hours after closure of an interventricular septal defect and incision of a pulmonary stenosis. Postoperative neurologic examination had not yet been performed. Grossly, the brain showed extreme congestion. Marked perivascular edema of the white matter was present histologically.

No correlations could be established between the pathologic changes and the electroencephalograms during perfusion. Of the 3 patients whose brains showed histologic changes compatible with hypoxia, 2 died during surgery. Their electroencephalograms during perfusion were not more abnormal than those of the 3 patients with histologically normal brains who died during or shortly after surgery. The significant data obtained from the 8 patients with brain involvement is summarized in Table 1. Review of similar data in the entire series failed to establish any correlations between preoperative and operative conditions and the presence or absence of cerebral complications.

TABLE 2. Possible Causes of Cerebral Complications with Extracorporeal Circulation

Emboli
Air or oxygen
Antifoam gel
Fibrin from filter
Other: Ivalon sponge particles, thrombi, valve calcifications
Inadequate perfusion
Complete heart block and other cardiac arrhythmias (postperfusion)
Over-oxygenation
Metabolic acidosis
Hypotension
Hemorrhagic diathesis
Heparinization
Hypofibrinogenemia
Thrombocytopenia
Superior vena caval obstruction due to faulty catheter placement
Pulmonary conditions leading to hypoxia
Atelectasis
Secretions
Other
Bacterial contamination
Hyperpyrexia
Miscellaneous
Elevated venous pressure
Hypovolemia
Hepatitis
Renal shutdown

DISCUSSION

Of 24 patients who underwent open heart surgery at this hospital in 1958, evidence of postoperative cerebral involvement was established in 8; 2 patients showed clinical and pathologic evidence, 1 had clinical abnor-

malities alone, and 3 had pathologic changes alone. Significant postoperative electroencephalographic alterations were present in 2 other patients.

Several possible means exist by which extracorporeal circulation may affect the brain. These are listed in Table 2. Hypoxic factors were probably important in 4 of the patients with cerebral involvement in the present series, and an induced coagulation defect was of significance in 1. Although a clinical diagnosis of cerebral embolization was entertained in 1 patient with an asymmetric electroencephalogram during perfusion and seizures and right hemiparesis postoperatively, this diagnosis was not supported by the autopsy findings of diffuse cortical hypoxic changes.

Experimental evidence indicating cerebral disturbances during extracorporeal circulation has been recorded. Thus, changes in the fluorescein blood-brain barrier have been demonstrated in animals undergoing cardiopulmonary bypass,[12] and cerebral oxygen consumption has been shown to be diminished during perfusion.[13,14] The brains of 60% of dogs dying immediately after perfusion have been reported to be edematous,[15] and increased brain volume (possibly related to superior vena caval obstruction) has been described in almost 50% of animals in another study.[14] Clinical neurologic changes such as ataxia, hemiparesis, and impaired responses to stimuli have been reported in animals after extracorporeal circulation,[16,17] especially when the perfusion is carried out under high pressures[18] or is prolonged.[19] Histologic evidence of cerebral embolization or infarction during cardiopulmonary bypass has been reported by some investigators[2,16,20] and denied by others.[3,21] Most of these experimental cerebral complications occurred more frequently with inadequate perfusion and with the inflow catheter in the carotid artery. The incidence of these complications also may be related to the type of oxygenator employed.

The increasing clinical application of extracorporeal circulation has led to several reports of its effects on the human brain. Torres and associates[7] performed pre- and postoperative neurologic examinations in 27 patients undergoing open heart surgery and found new postoperative abnormalities in 4. On the other hand, Patrick, Kirklin, and Theye[22] reported no obvious central nervous system abnormalities in any of 245 patients who survived surgery. However, it is possible that, if more detailed neurologic examinations had been performed, some abnormalities might have been revealed. Pre- and postoperative electroencephalographic studies have been reported by several workers,[7,8,12] and all have found new abnormalities after surgery. However, serial postoperative electroencephalograms have generally shown subsequent improvement. A review of the reported electroencephalographic alterations during perfusion and a discussion of the relative value of monitoring the electroencephalogram during cardiopulmonary bypass would be outside the scope of this communication. Nevertheless, the authors would like to call attention to the significance of an electroencephalogram that becomes asymmetric during surgery. This finding, which apparently has not been stressed in the literature before, is probably indicative of cerebral damage.

No reports of psychologic studies before and after open heart surgery have been found. The literature concerning neuropathologic changes in patients undergoing such surgery is also scanty, though several abnormalities,[4,15,20,22,23] including an Ivalon sponge embolus,[22] have been described. The relative lack of correlation noted in this study between perfusion times, operative complications, and the like, and the postoperative electroencephalogram and clinical neurologic abnormalities has been reported previously.[7,10]

The incidence of cerebral involvement in 8 out of 24 patients studied in this communication is spuriously high. The study was conducted during the first year of activity of the open heart unit, when a number of cases now considered to be poor risks were accepted for surgery.

It has not always been possible to determine whether the cerebral changes described in this study occurred during perfusion or in the immediate postoperative period. The possibility has not yet been excluded that some of these changes might occur in patients undergoing other cardiac or even intrathoracic surgery without the aid of a cardiopulmonary bypass.

SUMMARY

Cerebral involvement was noted in 8 of 24 consecutive patients who underwent cardiac surgery with extracorporeal circulation. The evidence for brain involvement was established on clinical grounds alone in 1 patient, by neuropathologic changes alone in 3, by both clinical and pathologic abnormalities in 2 patients, and by electroencephalographic changes in 2 others. No significant differences were noted between pre- and postoperative psychologic testing.

The observed incidence of neurologic complications after cardiopulmonary bypass may be high; a number of possible complications of open heart surgery exist which may affect the brain.

The authors are indebted to Mrs. Miriam Netzer for performing the Wechsler-Bellevue and Bender-Gestalt tests.

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Pilomotor seizures

Report of a case associated with a cerebral glioma

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PILOERECTION is a rudimentary and presumably worthless function in man, in contrast to its value to lower vertebrates, notably the fur bearers and the porcupine. The smooth muscle effectors (arrectores pilorum) are innervated by the sympathetic nervous system. Involvement of the pilomotor apparatus by a discharging lesion in the central nervous system is a rare event. The patient herein described is the first to our knowledge in whom paroxysmal piloerection was the principal manifestation of a cerebral tumor.

CASE HISTORY

A 53-year-old white housewife was admitted to the hospital on October 17, 1959, with a history of curious attacks for eighteen months. Each episode began with feelings of shortness of breath, mild nausea, and generalized heat, soon joined by sensations of tingling or coldness in the limbs. At first occurring mainly at night and awakening her from sleep, they became more severe and frequent in the four months before admission, occurring both day and night and lasting less than a minute, without alterations in consciousness. She had not observed when these began to include piloerection (goose flesh, cutis anserina, or horripilation), so strikingly evident in the attacks witnessed in the hospital and described below.

With one of her attacks four months before admission, she lost consciousness for approximately thirty minutes, remaining limp and without spontaneous abnormal movements. A similar episode occurred one month before admission, preceded by awareness of flashing lights in the left portion of her field of vision. Two days before admission, in her physician's office, she abruptly lost consciousness and was observed to have a major motor seizure, from which she recovered in ninety minutes. She also reported mild impairment of memory for the past eighteen months, without apparent progression.

She had had frontal or suboccipital headache intermittently for twenty years, often severe and lasting throughout the night, gradually becoming less frequent. Her past history was otherwise irrelevant, and the family history was noncontributory.

Examination revealed a slightly obese, alert, and moderately tense woman. Slight defects in recall of dates of events in the present illness were noted. Gross testing of the visual fields revealed a relative impairment of the left homonymous field, and tangent screen charting demonstrated slight constriction of the outer portion of the left field of each eye. The remainder of a detailed neurologic examination was essentially unremarkable, apart from observation on many occasions of the unusual attacks described below. Routine laboratory findings and stereoscopic roentgenograms of the skull were unremarkable. The electroencephalogram indicated a focus of irregular rhythms in the right temporal area, accentuated during one of her seizures (Fig. 1). Oxyencephalograms on her fifth hospital day revealed only partial filling of the posterior portion of the right lateral ventricle at the junction of the temporal and occipital horns. This portion of the ventricle was displaced laterally (Fig. 2A).

Observation of seizures. During the early portion of her hospital stay, the patient had many seizures, at least while awake, recurring

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at five- to fifteen-minute intervals. Some occurred shortly after a nurse or physician entered her room to ask about her progress. Each began with a sensation of ill-defined abdominal discomfort somewhat resembling nausea, followed within a few seconds by brisk piloerection visible over the limbs and slightly over the chest. No apparent change in skin temperature, color, or moisture was seen. With each attack, she usually began to breathe fairly rapidly and deeply. She stated that this was voluntary and based upon her feeling that the attack was thereby shortened. Her blood pressure rose moderately to approximately 140/90, with a mild tachycardia. Measurements of skin temperature by a thermocouple placed over one forearm before, during, and after a seizure revealed no detectable change. Throughout each episode, she remained fully alert and able to understand and to converse freely, although manifestly distressed and apprehensive of progression to unconsciousness and a convulsion.

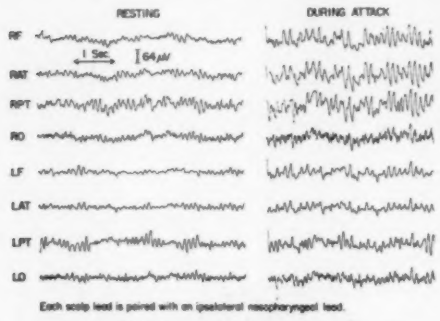
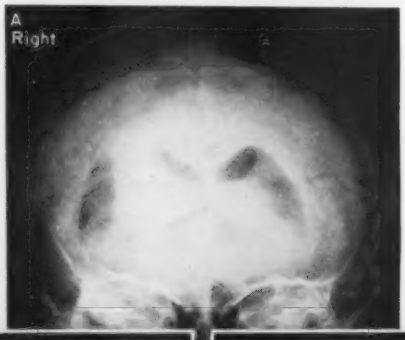


Fig. 1. Electroencephalogram made preoperatively, indicating abnormal wave forms of theta frequencies in the right temporal area at rest, increased in amplitude during a pilomotor attack

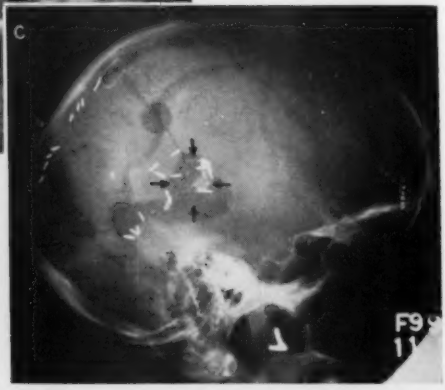
Dilantin and phenobarbital were prescribed on the fourth day, and, either as a result of these medications or the oxyencephalograms

Figure 2

[A] Preoperative oxyencephalogram in posteroanterior projection demonstrating lateral displacement of the posterior portion of the right lateral ventricle



[B and C] Postoperative posteroanterior and lateral roentgenograms of skull indicating position of tantalum dust (outlined by arrows) inserted deep into operative site near mesial limit of tumor



on the following day, the attacks soon ceased, although the left homonymous field defect became virtually complete. Five days after the oxyencephalograms, an operation revealed a large solid tumor deep in the right cerebral hemisphere at the junction of the parietal and occipital lobes. It extended down toward the thalamus and the basal ganglia. A large portion was removed, and tantalum dust was inserted into the depths of the wound to permit radiologic demonstration of the extent of the excision (Fig. 2B and C). On histologic examination, the tumor proved to be glioblastoma multiforme.

The patient's postoperative course was uneventful and seizure-free to the time of discharge from the hospital, the complete left homonymous hemianopsia persisting. She was maintained on Dilantin alone, 100 mg. four times a day.

At home under the care of her family physician, the patient at first did well. She had only two further episodes, which were by description similar to the "pilomotor seizures" noted in the hospital. However, on December 27, the day after the second of these attacks, she lost ground rapidly, becoming lethargic and confused, then vomiting repeatedly. She was admitted to the local hospital three days later. Shortly afterward, she had a grand mal seizure and thereafter remained stuporous; spastic left hemiplegia gradually developed. She was afebrile until the last two days of life, when her temperature rose steadily, without manifest signs of infection in the lungs or urinary tract. She died on the twenty-eighth hospital day. Permission for an autopsy was not granted.

DISCUSSION

In lower animals, piloerection assists regulation of body temperature. A major center for control lies in the posterior hypothalamus, in the same area as that controlling shivering and cutaneous vasoconstriction, mechanisms which also enhance or conserve body heat.[1,2] In the porcupine, quill elevation represents a highly developed form of piloerection modified to defend against assault. Stimulation experiments in this animal by Richter and Langworthy[3] revealed that quill erection could be evoked from several areas in the region of the optic colliculi and the medulla. These observations apparently represent the only recorded instances of experimental piloerection produced by stimulation of the brain stem.

Less is known of higher level (cerebral) control of piloerection. Penfield[4] reports that he was never able to evoke this effect from stimulation of any area of the human cortex. In cats, however, a bilateral pilomotor response was occasionally noted by Kaada, Andersen, and Jansen[5] in stimulation experiments on the amygdaloid nuclear complex. In the monkey, stimulation of the cingulate gyrus by Ward[6] produced piloerection together with other autonomic responses. Evidence that the cerebrum exerts an inhibitory effect upon the pilomotor system will be mentioned below.

Observations of piloerection as an epileptic manifestation have been few. Penfield[4] has commented that, in his experience, this reaction is occasionally part of a more generalized seizure. He reports in detail the case of a young adult with a large astrocytoma of the entire left temporal lobe who had seizures of various types, some of which included numerous autonomic responses. A single mild seizure observed on the day of death included generalized flushing and then piloerection over the thorax and legs. In his well-documented instance of "diencephalic epilepsy," noted in a woman with a tumor within the third ventricle, the seizure manifestations were again numerous and somewhat varying. In several, at the close of an attack and during Cheyne-Stokes respirations, piloerection was observed during the hyperpneic phase of the respiratory cycle. Piloerector responses were observed in one other patient and presumed in another, accompanying brief autonomic seizures of unknown cause.

A few earlier clinical notes of the past century are little more than provocative. Féré[7] described in 1896 a complex illness in a man who had seizures of several types beginning in infancy. Many episodes, some with and some without unconsciousness, were marked by pallor, coldness, sweating of the limbs, and generalized goose flesh (*chair de poule*). The limited clinical data offer no clues as to the source of the disorder. The same author wrote in 1904[8] of a remarkable illness, dating from adolescence, in a man of 53. A typical attack

was observed to begin with pallor of the right half of the face and piloerection in this same area and also over the right side of the neck and upper limb, lasting approximately twenty minutes; these features were soon accompanied by right homonymous hemianopsia, hemicranial headache centered below the right eye, slight difficulty in articulation, and jerking movements and paresthesias in the right hand. Féré considered this disorder to be an instance of "ophthalmic migraine," but, in retrospect, a vascular anomaly or other lesion of the left parietooccipital area can reasonably be suspected.

More pertinent to the patient of the present report, but offering no useful data, is the fragmentary history cited by Hutchinson[9] in 1897, describing a man with paroxysms of generalized piloerection, sometimes several a day, beginning in mid-adult life and joined within a year by generalized seizures. He was reputed to have had syphilis. The outcome is unknown.

The site and mode of excitation of the pilomotor system in the patient herein reported remain undetermined. Piloerection was the most striking manifestation of her attacks and was clearly dissociated from other phenomena with which it is ordinarily related, that is, cutaneous vasoconstriction and shivering. Also, it was not secondary to paroxysmal sweating with consequent cooling of the skin. The moderate elevation in blood pressure observed during the attacks is of uncertain significance in view of the manifest apprehension which the patient reported with each episode. Although some of the symptoms of her earlier attacks, notably the paresthesias in the limbs, may have been associated with hypocapnia caused by hyperventilation, this mechanism could not account for the pilomotor manifestations witnessed in the hospital. Hyperventilation of moderate intensity accompanied the attacks but clearly followed the onset of the piloerection; between attacks, the respiratory patterns were normal.

The tumor undoubtedly penetrated the deeper portions of the right optic radiation, but its full extent could not be accurately determined at operation. It may have reached the vicinity of the posterior hypothalamus or connections between the amygdaloid portion of the right temporal lobe and the hypothalamus. No evidence existed that it directly involved the amygdala or the cingulate gyrus, areas some distance away.

It seems possible, therefore, that the attacks of piloerection in this patient were curiously restricted seizure discharges from the hypothalamus or other areas of the limbic system, induced in some way by the deep-lying tumor. This assumption at once raises the familiar and troublesome question: By what mechanisms can lesions of the brain provoke episodic discharge? The effect of the tumor may have been one of direct stimulation of corticohypothalamic pathways. It may, on the other hand, have been quite indirect, interrupting these connections and permitting paroxysmal release of lower centers from inhibitory control.[10] Relevant to the latter hypothesis is experimental and clinical evidence that some portions of the cerebral cortex exert a suppressive influence on the pilomotor system and that removal of this inhibition may facilitate pilomotor reactions. Kennard is reported by Fulton[11] to have demonstrated an exaggeration of pilomotor responses after cortical ablations in the monkey, and the rage response so readily evoked by section of tracts connecting the frontal lobes and the hypothalamus includes vigorous piloerection.[12] Furthermore, in two patients with hemiplegia due to cerebral lesions, Brickner[13] observed marked piloerection on the hemiplegic side after "emotional" stimuli, whereas the piloerection produced reflexly by midline cutaneous stimulation was entirely symmetric.

From such data, it might even be argued that the episodes of piloerection in our brain-damaged patient were not, in the strict sense, seizures but merely indicators of special susceptibility to previously trivial and subliminal stimuli. Her attacks would thus have represented the augmented responses of a pilomotor system continuously deprived of inhibitory control.* Yet, it is more tenable to consider that this patient's episodes of piloerection were, by

*An analogy can be drawn between such a state of altered subcortical excitability and that of "pseudobulbar palsy," in which the emotional outbursts to trivial or even inappropriate stimuli are attributed to interruption of corticobulbar connections, with release of lower centers controlling emotional expression. Such paroxysms are not ordinarily classified as "epileptic."

commonly accepted criteria, true seizure manifestations. The attacks were usually quite spontaneous, were shown to be accompanied by an accentuation of a focal cerebral dysrhythmia, and were for several weeks suppressed by anticonvulsant medication after partial resection of the tumor. Her illness included, moreover, a few unequivocal cerebral seizures accompanied by loss of consciousness and, shortly before admission, by convulsive movements.

In short, whether they resulted from paroxysmal stimulation or sudden loss of inhibition of subcortical autonomic centers, the pilomotor manifestations in our patient are here viewed as genuine epileptic phenomena.

Apart from these problems of pathogenesis, the extreme frequency of the pilomotor seizures late in the course of the illness and the apparent tendency of some attacks to be provoked by the attendance of staff members indicate a highly labile discharging mechanism. On a less impressive scale, this excitability is evident in everyday experience. The ease with which the normal pilomotor reflex is evoked by cold, stroking of certain portions of the body, or "emotional" experiences varies widely from individual to individual, but, in some, this response is a most sensitive one. The emotional reactions with which it may be associated are of many kinds, commonly unpleasant or even frightening, yet in some individuals predominantly thrilling or spine-tingling in a pleasureable way. Maxwell[14] refers to a woman of his acquaintance who was subject to "waves of goose flesh on listening to pathetic music." Darwin,[15] from observation of his own friends, considered this behavior to be commonplace. A few individuals, of whom two have been studied with care,[14,16] possess the singularly useless faculty of voluntary piloerection, a throwback, perhaps, to the behavior of the "fretful porcupine."

SUMMARY AND CONCLUSIONS

A patient is described in whom frequent brief episodes of generalized piloerection were associated with a deep parietal glioblastoma. Past experimental and clinical evidence indicates that piloerection as a seizure manifestation has no precise localizing value but that the site of excitation, or release from inhibitory control, is probably close to the hypothalamus or some portion of the limbic system.

Assistance was given in this study by the referring physician, Dr. Samuel L. Elfmon, and by Dr. Keith S. Grimson.

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Familial idiocy with spongy degeneration of the central nervous system of van Bogaert–Bertrand type

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In 1949, van Bogaert and Bertrand[1] presented a comprehensive clinical and pathologic study of a disease occurring in early infancy designated as "Idiotie familiale avec dégénérescence spongieuse du névraxe." The authors intended to distinguish this disease from the clinically similar progressive diseases of Tay-Sachs and Krabbe. Previously, a few cases resembling this condition have been published as Schilder's disease,[2] Krabbe's disease,[3] or familial diffuse sclerosis.[4]

Subsequent observations have been reported under various names: "Ödemkrankheit des Zentralnervensystems im frühen Kindesalter,"[5] "Spongy Degeneration, a Subtype of Diffuse Sclerosis,"[6] and "Spongy Type of Diffuse sclerosis."[7] In 1958, de Vries, van Bogaert, and Edgar[8] added 5 more cases under the title: "Idiotie familiale avec dégénérescence des centres nerveux (Maladie Oedémateuse progressive cérébrale de la première enfance)."

A case of this disorder will be presented, and the clinical features of 2 siblings, not personally observed by the authors, will be mentioned. Comparisons with previously published cases will be made, and the basic disease process discussed. This is the first case in the American literature and the first in the world literature to be diagnosed by brain biopsy during life.

CASE REPORTS

The patient, S. S., is the youngest of 5 female siblings. Both parents are healthy. They are the second generation descended from German immigrant stock. No evidence of consanguinity or Jewish ancestry in the family exists. No neurologic diseases have been recorded. The first and fourth siblings have been examined by one of us (P.L.E.) and found to be normal. The second and third siblings were diagnosed as having cerebral palsy and died at ages 7 and 21 months, respectively.

The *second sibling* was born six weeks prematurely after an uncomplicated labor. Her birth weight was 6 lb., 2 oz. From birth, the baby assumed an extensor spastic position of the lower extremities with flexion of the upper extremities and opisthotonus. At 5 weeks, she refused food and became progressively more lethargic. She was admitted to University Hospitals at 3 months of age. On physical examination, she was pale and poorly developed. Her length was 53 cm., the head was 35 cm. in circumference, and her weight was 6 lb., 8 oz. The parietal bones were bossed, and the anterior fontanelle was open and soft. Roving eye movements suggestive of blindness and bilateral optic atrophy were noted. The deep tendon reflexes were brisk with bilaterally positive signs of Babinski. All extremities were severely spastic, especially in the antigravity muscles. Hands and feet tended to be held in flexion, although there were occasional spontaneous flexion-extension movements. The arms were held in extension and abduction, and the pectoral muscles were markedly spastic. The head was difficult to rotate because of spasticity. There were no Magnus and de Kleijn reflexes.

Routine urine and blood studies were within normal limits. An electroencephalogram was normal for the age. Roentgenograms of the

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Figure 1

Fig. 1. Characteristic flexion spasticity of upper extremities and extension of lower extremities. Spontaneous Babinski in both feet. Age, 17 months

Fig. 2. Hypotonicity of cervical muscles. Hyperextension of lower extremities. Enlargement of head. Age, 17 months

Figure 2

skull were normal. The clinical impression was cerebrospastic infantile paralysis with grade IV optic atrophy. A pneumoencephalogram was recommended but refused. Four months later, the child died in a state of inanition and respiratory failure at the age of 7 months.

The *third sibling* was not examined. The mother describes her as having been similar to our patient. From the second month, she appeared to be blind, showed no mental development, and was never able to sit. Her neck muscles were more flaccid than those of S. The head did not seem enlarged. This girl died of pneumonia at the age of 21 months.

The patient, (S. S.), was first seen at 8 months of age because of poor development, spasticity of the extremities, enlarged head, and lethargy. Her birth at term had been uncomplicated, and the birth weight was 10 lb., 4 oz. At the age of 2 months, the child was noted to have weak neck muscles. She was unable to turn from the prone to the supine position and did not respond to light. At 4 months, increasing macrocephaly was obvious.

Physical examination at 8 months of age showed a lethargic and pale but well nourished and hydrated child. The head measured 49.5 cm. in circumference, and the length was 75 cm. She weighed 21 lb. Hair, nails, and teeth were normal. The palate was high-arched. She did not follow moving objects, and it was doubtful if there was any response to light. The optic disks were pale, and no cherry-red spot was seen at the macula. The cranial nerves were not otherwise remarkable. The sucking reflex was present. Spasticity was evident in all extremities with hyperactive deep tendon reflexes and positive pyramidal tract signs. The arms tended to be held in a slightly abducted position with flexion at the elbows and pronation at the wrists. This position was characteristic (Fig. 1). At times, sudden generalized spasms occurred during which the lower extremities were extended at the knees and ankles and the upper extremities flexed at the elbows and wrists. These episodes lasted for a few seconds and could be elicited by many types of stimuli. A sensory examination was not successfull. The cervical muscles were extremely hypotonic and remained so despite postural

changes (Fig. 2). Magnus and de Kleijn reflexes were not present. Abdominal reflexes were absent. During sleep, the child's position was normal.

The routine laboratory studies of urine and blood were within normal limits. Urinary heavy metal levels were lead, 0.03 mg. per liter; copper, 0.095 mg. per liter (normal, less than 0.03); and zinc, 1.65 mg. per liter (normal, less than 0.07). Urinary porphobilinogen was 1 gm. per liter, and delta-amino-levulenic acid was 5 mg. per liter. Cerebrospinal fluid examinations were normal. A Sabin dye test for toxoplasmosis was negative. The electroencephalogram had many 1- to 2-cps waves of 100 to 250 μv. in amplitude, some of which were associated with spikes spreading widely over the cortex; the major abnormality was located in the left temporal area. Paper electrophoresis studies of serum and urinary proteins were within normal limits. A pneumoencephalogram disclosed slightly enlarged ventricles and no subarachnoid filling over the hemispheres. The fourth ventricle was poorly visualized. The assumed diagnosis was communicating hydrocephalus with possible chronic adhesive arachnoiditis. On this basis, a subarachnoid-peritoneal shunt was performed in the lumbar region. The patient's postoperative course was poor, and, because of increasing concern that a posterior fossa lesion might be present, a suboccipital craniotomy was performed. During the dissection of the cerebellar vermis, the tissue was abnormal in color and soggy and gelatinous in texture. Cerebellar tissue was obtained from the right and left hemispheres for study. Because of the suspicion of a systemic disease, a cortical biopsy was performed on the left occipital lobe. The patient recovered from the operations and was discharged.

Seven months after surgery, there was slight lessening of the spasticity and she was able to move her head feebly. Head size had increased to 50.5 cm. Study of vision and audition suggested partial amblyopia, and there was response to loud noise. Sudden movements of the head sometimes caused spontaneous rapid nystagmoid movements of the eyes. In other respects, the neurologic examination was not remarkably different from the one recorded earlier. A sagittal sinogram was normal. A second biopsy of cerebral cortex was performed. The patient was placed on a program of oral urea in daily doses of 0.5 mg. per kilogram for five days out of each week. This program was followed for the next twelve months.

Visits during 1958 and 1959 indicated the following changes. The head increased to 51 cm. in circumference. At 31 months of age, the weight was 26 lb. and length was 82 cm. Magnus and de Kleijn reflexes were now demonstrable. Exaggerated reaction to loud noise was manifest by extensive spastic jerks of all extremities followed by clonic movements of both arms in a flexed and adducted position.

The only mental progress is that she now seems to recognize and respond to members of the family.

PATHOLOGY

Tissues from the *first* craniotomy were pale and gelatinous in consistency, with no distinct demarcation between gray and white matter. They were embedded in paraffin, and sections were stained by the hematoxylin and eosin, Nissl, von Gieson, Holzer, Bielschowsky (reticulum), Bodian, Weil, and Schiff–periodic acid methods.

In the *cerebellum*, the most striking feature was an extensive vacuolization resulting in conspicuous disruption of the subcortical white matter and the lamina dissecans (Fig. 3). The outer and main granular layers were less involved, and the molecular layer was scarcely involved. Cystic spaces were formed, the largest of which measured 192 μ (Fig. 4). The various staining technics demonstrated no substance within these spaces. Many Purkinje cells were displaced toward the molecular layer over distances of 1 to 2 cell diameters. They were regular in appearance with only a few cells showing shrinkage or containing very small vacuoles, especially at the border of the nuclear membrane.

Another prominent finding was an increase in the number and hypertrophy of astroglial cells in the subcortical white matter and the Bergmann glial layer (Fig. 3). The cytoplasm of subcortical astrocytes in hematoxylin-eosin–stained material measured 2 to 3 times the size of the nucleus. Little fiber production was seen. In the subcortex, the astroglial cells were pre-

dominant; oligodendroglial cells and degenerating glial cells with poorly staining, shriveled, and indistinct nuclei were scattered between the astrocytes. Due to less vacuole formation, the glial cells deeper in the white matter were more concentrated and the predominant cell type was a normal-appearing oligodendrogliocyte. No gitter cells were seen.

The third impressive feature was the rarity of myelin sheaths in the subcortical white matter. A few widely spaced sheaths showed marked beading or focal loop formations (Fig. 5). The sheaths varied in thickness from 1.4 to 3.2 μ in the beaded portions. Fragments of fenestrated myelin were seen. Deeper in the white matter, the myelin sheaths appeared to be of normal density but also showed beading and loop formation. The sheaths extended in all directions without parallel alignment.

The number of axis cylinders was not decreased. Their diameter varied from 0.5 to 0.8 μ, and they often were seen to curve along the periphery of subcortical vacuoles (Fig. 6A). Many cylinders showed beading or varicosities and changed directions abruptly several times over short distances (Fig. 6B).

The leptomeninges appeared normal. Perivascular fibrosis, characterized by the presence of argentophile fibers but the absence of collagen, was prominent in subcortical vessels. Neither capillaries nor larger vessels showed endothelial changes.

In the *cerebrum*, there was also a conspicuous vacuolization of the tissues leading to a spongy appearance of subcortical white matter, including the U-fibers; these changes were not as extensive as in the cerebellum (Fig. 7). The long axes of the oval-shaped vacuoles were parallel to the surface of the brain. Involvement varied in different areas of the cortex. In some, the vacuolization extended throughout the entire cortex and the Virchow-Robin spaces as well as Held's subpial space were markedly distended. The cortical vacuoles measured 16 to 32 μ, and the subcortical vacuoles measured 32 to 48 μ. The cortical vacuoles appeared empty or contained capillaries, nerve cells, or glial cells in the center or at the periphery, where they followed the curved surface of the vacuole. At times, only eosinophilic or basophilic debris or cytoplasmic bridges of cells were found in the vacuoles.

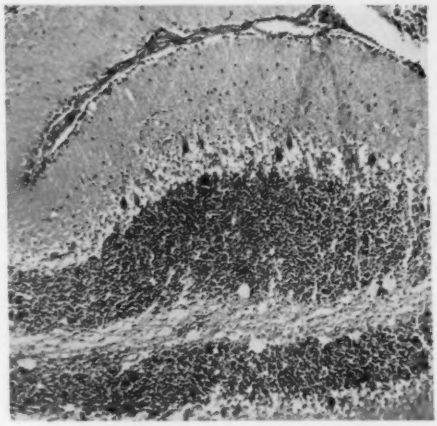

Fig. 3. Extensive vacuolization of lamina dissecans and subcortical white matter. Displacement of Purkinje cells, numerical increase of Bergmann glia. Hematoxylin and eosin. × 105

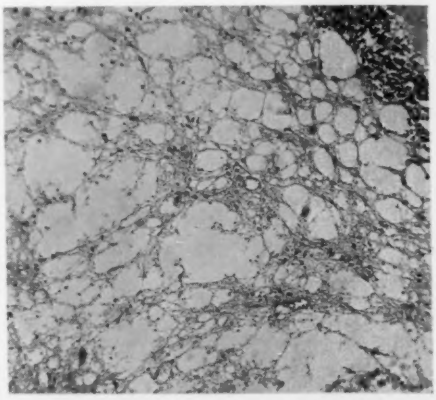

Fig. 4. Extreme vacuolization (largest vacuole 192 μ) white matter of cerebellar folium. Hematoxylin and eosin. × 105

The number of astroglial cells in the cortex was increased; some of their nuclei showed changes characteristic of the Alzheimer II type, and 2 or 3 often were grouped together (Fig. 8). Nuclear diameters were 6.5 to 8 μ. In the subcortical white matter, hypertrophic astrocytes with rich perinuclear cytoplasm and very long and thick processes comprised approximately 50% of the glial population. Little

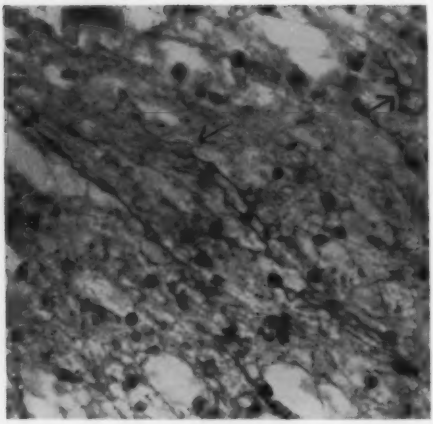

Fig. 5. Scarcity of myelin sheaths; beading and loop formation indicated by arrows. Weil stain. × 650

astroglial fiber production was noted in the subcortex and none in the cortex. The myelin pattern was severely defective; very rarely, a beaded sheath was seen longitudinally in the subcortical white matter. A moderate number of myelin rings, 2 to 3 μ in diameter, were found scattered at the tissue bridges. No gitter cells or metachromatic material (thionine stain) was present. The axis cylinders were similar to those in the cerebellum.

The leptomeninges showed no abnormality. Cortical arterioles seemed slightly thickened and had narrow lumina. Subcortical veins were markedly dilated and had a corrugated inner surface in places (Fig. 9A). Perivascular fibrosis was evident in several subcortical vessels (Fig. 9B). No inflammatory infiltrates were seen. The nerve cells were not reduced in number, but most cells were shrunken and showed cytoplasmic and nuclear hyperchromasia (Fig. 8). The Nissl substance was preserved and dense.

Tissues from the right and left occiptal lobes were obtained at the second craniotomy. Frozen sections were stained with hematoxylin and eosin,[9] Sudan IV, and Schroeder methods. Paraffin sections were stained as previously; 2 unfixed pieces of cerebral subcortex were used for moisture determinations and were dried at 110° C. for two days. These pieces were matched by controls from similar locations obtained at autopsy from a child of the same age. The weight losses were right occipital lobe, 84.8% (control, 75%) and left occipital lobe, 86.9% (control, 74%).

In the cerebral cortex and subcortex from the *second* craniotomy, the following alterations were found. A nearly diffuse, very fine porosity of the "background" tissue was seen in the cortex. A tendency for nuclear or cytoplasmic enlargement in glial as well as in

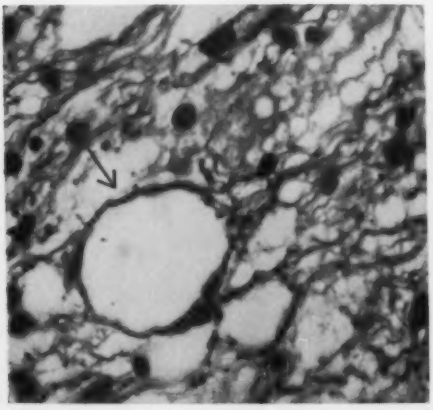

Fig. 6A. Axiscylinder, following outline of vacuole, indicated by arrow. Bodian stain. × 900

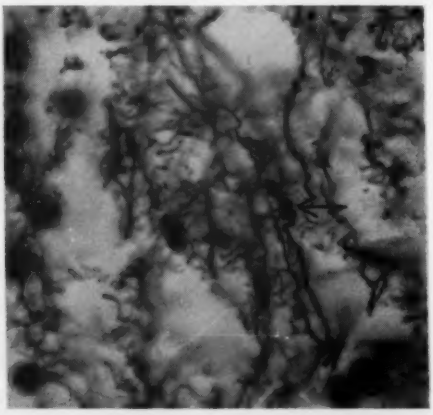

Fig. 6B. Scalloping and directional changes in axons. Varicosity indicated by arrow. Bodian stain. × 900

nerve cells, with difficult differentiation, obscured the structural pattern of the cortex. Astroglial nuclei were 8 to 10 μ in paraffin sections. Giant glial nuclei with astrocytic chromatin were scattered singly and had diameters of 5 to 8 times those of the usual cortical astrocyte. Only a small number of nerve cells were shrunken; most of them showed such extensive vacuolization of the cytoplasm that only cytoplasmic bridges remained and the nucleus assumed a polygonal shape from pressure. Nuclei of these nerve cells measured 8 to 10 μ, and the cell bodies were 16 to 20 μ. No Nissl substance was seen in these cells. Oligodendroglial cells often were in a state of swelling with pyknotic nuclei. Rod cells occurred in groups in a patchy distribution at areas where the nerve cell population was obviously decreased. Sudanophilic granules were present in their cytoplasm. Capillary endothelial cells were prominent and swollen, and capillary lumina were seldom seen.

In the subcortical white matter, sudanophilic droplets were found at 15 to 20 astroglial cells per high power field. Very little lipid was noted in adventitial or endothelial cells. Gitter cells were not seen. The tissue spaces in frozen sections were essentially the same size as those in paraffin sections. In Schroeder stains, dust-like hematoxylin-staining material (myelin?) appeared diffusely in the tissue bridges, as well as intracytoplasmically in glial cells most likely sudanophilic astrocytes. In paraffin and especially in frozen sections, regressive changes were noted in glial cells presumed to be oligodendroglia. The changes included perinuclear and intranuclear vacuoles (0.8 to 4 μ) with several often in one cell, disfiguration and hyperchromasia of nuclei, and a faded or moth-eaten appearance of nuclei (Fig. 10).

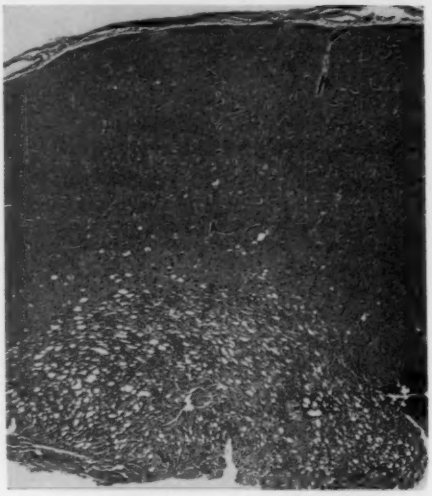

Fig. 7. Vacuolization of cerebral subcortex, extending through U-fibers into lower cortex. Hematoxylin and eosin. × 30

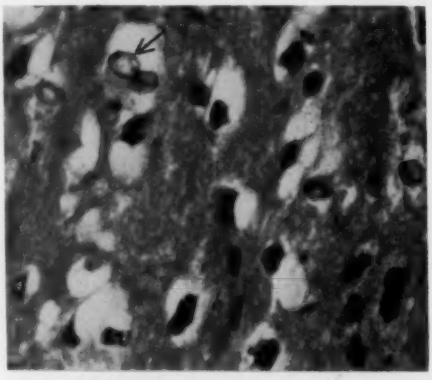

Fig. 8. Hypertrophic astroglial cells, cerebral cortex; Alzheimer II change indicated by arrow. Marked vacuolization. Hematoxylin and eosin. × 630

DISCUSSION

In a systematic research on amaurotic familial idiocy occurring in Jews, van Bogaert and Bertrand found their first case of this disorder which they distinguished from Tay-Sachs' disease.[1] As additional cases were published, it became evident that the disease was not limited to Jews. The following discussion will include our patient and her 2 siblings and those cases extracted from the literature. Of the 9 families[1,2,5–8] from which diseased children were reported and our family, 5 were Jewish and the raciality was not mentioned in 4. The family in this case has no known Jewish ancestry, and the parents are descended from German immigrant stock. Consanguinity was

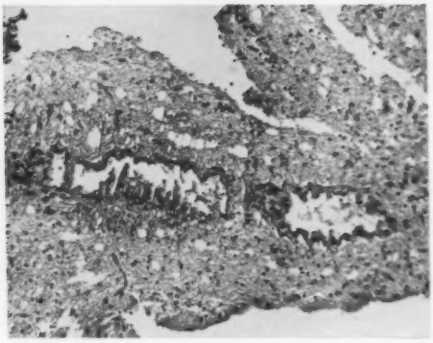

Fig. 9A. Dilated subcortical vein (cerebrum) with corrugated inner surface. Hematoxylin and eosin. × 105

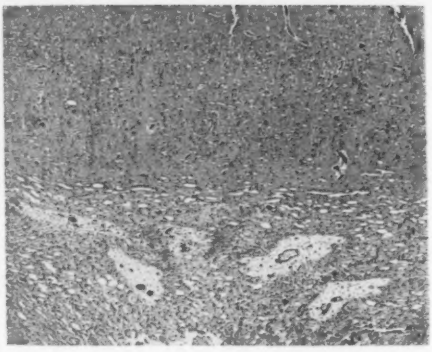

Fig. 9B. Perivascular fibrosis observed in the cerebral subcortex. Hematoxylin and eosin. × 30

present in only 1 family, in which the parents were first cousins. There was no blood relationship in 2 families, and no significant remarks were made in the remaining families. In no instance had an infantile spastic disorder been present in earlier generations. The sexes have been involved equally. The number of afflicted children in 1 family was highest in the Haty family[8] with 3 of 5 siblings affected. In 8 families from which data are available, 14 of 22 siblings were involved. However, among 16 children considered to be afflicted, a clinical and pathologic diagnosis of the disease was obtained in only 8, although 8 more were included by inference, on the basis of either purely clinical (7 cases) or purely pathologic (1 case) features.

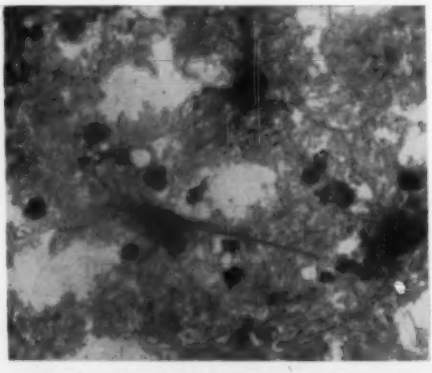

Fig. 10. Degenerated glial cells (intra- and perinuclear vacuoles) in spongy subcortex. Fibrous astrocytes with long, thick processes. Frozen section. Hematoxylin and eosin. × 630

The mother in our family had only normal pregnancies, and this was true for the majority of the other cases where this information was included. Nephropathy was mentioned in 1 case, and liver trouble early in pregnancy was noted in another. A breech presentation with delivery after twenty-four hours of labor[1] was the only deviation found in the delivery notes of 12 cases. Prematurity, as suspected in 1 sibling of our family, was noted in only 1 other case (7 months).[1]

The clinical features of our patient were the same as described by van Bogaert and Bertrand.[1] She also had megalocephaly, which had been noted in 10 other cases. Canavan's case[2] was published especially to distinguish "macrocephalus due to diffuse degeneration from hydrocephalus or tumor." Among the 4 cases in which a tentative diagnosis of hydrocephalus was made, only in our patient were surgical procedures performed.

Except for marked constipation, dermatographism, and pallor, our patient did not show signs of autonomic nervous system dysfunction. Special attention has been given to autonomic dysfunction by de Vries, van Bogaert, and Edgar.[8] In 2 of their cases, episodes of profuse sweating, vomiting, a tendency to "collapse," hypothermia, and hyperthermia were noted. Vomiting was mentioned in 2

other cases,[1,2] in 1 being associated with constipation. Pallor of the skin was described in 1 case[5] besides our patient and 1 sibling.

The onset of the disease was noted invariably within the first nine months of life with some emphasis on the second month, as in 2 of the infants in our family. The earliest manifestation occurred in the second sibling of our family who was born with spastic extension of the legs. In 2 other cases,[7,8] the onset was immediately after birth and during the first days of life. Thus, while some of the infants never developed normally, others deteriorated after what seemed to be a normal initial development. The first presenting clinical symptoms in almost all cases were motor deficiencies of atonia, spasticity, or both. Enlargement of the head, if present, became clinically evident between the fourth and ninth months, with a maximum increase of 5 cm. in one month.[2]

Death has occurred at an average age of 18 months, with a range from 7 months to somewhat over 3 years.[1]

Because of the uniqueness of the pathologic picture in this disease, the diagnosis in our case was definitive on the small amount of tissue obtained surgically since the process was diffuse and involved 3 widely separated portions of the brain.

The gross sogginess, gelatinous appearance, and soft consistency of the brain tissue in our case were so obvious that a degenerative disease was assumed during the biopsy. The terminology used by other observers for these prominent features includes soft, retractile, mucoid, transparent, gelatinous, and "like a sponge soaked with water."

Brain weights, when recorded, were regularly increased, varying from 820 gm. at 8½ months (normal, 730)[10] to 1,890 gm. at 16 months (normal, 1,010).[10] All gross pathology reports included descriptions of the ventricles, but only air studies of the ventricles are mentioned in some clinical reports. Enlargement was denied in 3 cases,[2,5,7] thought slight in 2 cases, [1,8] and stated as being present without giving the degree in 2 cases.[6,8] An 86.9% water content was found for fresh white matter in our case. However, Blackwood and Cumings[6] reported the remarkably high value of 92.2% water in fresh white matter and 85.6 and 87% for cortical and subcortical gray matter, respectively. One study[8] after eighteen months' fixation showed twice as large a water content for the centrum ovale as in a 66-year-old male control.

The classical microscopic findings as described by previous investigators could be identified in the cerebral and cerebellar cortex and subcortex. In previously studied cases, the findings were more evident in the cerebrum, but, in our case, the cerebellar involvement seemed more impressive. The other authors have found characteristic involvement also in the centrum ovale, the basal ganglia to a lesser degree, the optic nerves and tracts, and the cervical and thoracic levels of the spinal cord. Sponginess is the most widespread single characteristic reported. The clinical data in our case suggest that the extrapyramidal structures, optic nerves, and, possibly, the brain stem may be involved in addition to the cortex and subcortex.

In previous pathologic reports, there is some discrepancy concerning the amount of fat found in the nervous tissues. In 3 cases, no fat was seen.[1,2,7] In 2 cases, small amounts were present in adventitial cells.[5] In 1 case,[6] many globules of lipid were noted, and, in 2 cases,[8] fat droplets were seen free, perivascularly, within round cells, or included in oligodendroglial cells in the subcortical tissue bridges. In this study, considerable numbers of subcortical glial cells, probably astrocytes, contained sudanophilic inclusions. Since there was no corresponding amount of lipid in association with blood vessels, it is considered that this lipid might have been derived from degeneration of mitochondria which may result from a disturbance of intracellular metabolism. Duncan and Nall[15] have recently reported evidence of conversion of mitochondria to lipid inclusions from electron-microscopic observations on tissue culture cells.

The histologic features of tissue hypoxia noted to a moderate degree in the second cortical biopsy have not been reported previously. It is possible that the focal loss of nerve cells and the rod cell proliferation were secondary to the proximity of this tissue sample to the first biopsy site.

In considering the over-all picture of the disease, the basic process is consistent with progressive water accumulation in the central

nervous system tissues. This view is suggested also by van Bogaert and Bertrand[1] and Mayer.[5] Although various abnormalities have been noted clinically before enlargement of the head and some infants have died without enlargement, the edema may have been present in the tissues before the obvious expansion of the skull. In our microscopic observations, all criteria[11–14] of chronic edema with low protein content were found. The extensive cytoplasmic vacuolization of nerve cells from the second biopsy as well as peri- and intranuclear vacuolization of subcortical cells, not previously reported, have raised the possibility of intracellular edema[16] in addition to the interstitial edema. Some of the tissue vacuoles may have resulted from a rupture of cell membranes after extreme water uptake, or retention, or from release into the cytoplasm.

The deficiency of the myelin pattern is most likely secondary to the water retention in the nervous tissues. The myelin-destructive effect of edema is well recognized. Electron-microscopists have postulated that myelin synthesis may depend solely or largely on the intact metabolism of glial cells, especially oligodendroglia.[17] The maintenance of myelin being dependent equally on these cells has been postulated by other investigators.[16] Lumsden,[16] in his views regarding principles of demyelinization, reaches the conclusion that disturbed osmoregulation at the oligoglial level may lead to water retention between myelin lamellae and also between myelin and axoplasm. From the distribution of the myelin deficiency, the internal capsule myelin being mostly preserved, from the general scarcity rather than degeneration of myelin, and from the scantiness of lipid transport to perivascular spaces and endothelial cells, the problem is one mainly of failure in myelin synthesis at the sites of earliest and major edema. This is associated to a lesser degree with demyelinization when the edema progresses into previously uninvolved white matter where myelin formation is already complete.

SUMMARY

A case of familial idiocy with spongy degeneration of the central nervous system of the van Bogaert–Bertrand type has been presented.

The salient clinical features of this disease are onset in early infancy, atonia of the neck muscles, hyperextension of legs and flexion of arms, blindness, severely defective mental development, megalocephaly, and death at an average age of 18 months.

Principal pathologic findings include a spongy degeneration of the white matter extending through the U-fibers into the cerebral cortex, a severely defective myelin pattern, proliferation of astroglial cells, presence of Alzheimer II cells, and lack of glial sclerosis.

Patient S.S. was still alive without significant clinical change on September 23, 1960, at the age of 4 years, 1 month.

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Diagnosis and treatment of myasthenia gravis in infancy, childhood, and adolescence

A study of 51 patients

J. Gordon Millichap, M.D., and Philip R. Dodge, M.D.

WILKES, in 1877, and Erb, in 1879, have been credited with the first description of myasthenia gravis in children.[1] The transient type of myasthenia, which occurs in infants born to mothers with the disease, was noted by Viets[2] in 1939 and was described in detail by Strickroot, Schaeffer, and Brown[3] in 1942. Bowman,[4] in 1948, was first to report persistent symptoms of myasthenia gravis in an infant whose mother was unaffected by the disease.

It is of some interest that, in 1940, Kinnier Wilson[5] had written that "children's cases were both infrequent and dubious," but, since the introduction of the Prostigmin test in diagnosis,[6,7] many reports of the disease in infants and children have been published. The largest series has been that of Teng and Osserman,[8] who in 1956 described 21 patients; 2 of these cases were recognized as the transient neonatal type of myasthenia, and 19 were classified as juvenile cases, with symptoms beginning at birth or up to 17 years. Cases culled from the literature at that time totalled 196. In a more recent publication,[1] Osserman reported 8 additional cases of the juvenile type.

The present report consists of a follow-up study of 51 patients whose symptoms began before they were 17 years of age. Thymectomy was performed in 21 patients in this series, and the results of the operative treatment have been evaluated and compared, as far as possible, with those of drug treatment alone.

CLINICAL MATERIAL

Of 447 patients who attended the Clinic for Myasthenia Gravis at the Massachusetts General Hospital between 1935 and 1959, 51 experienced their first symptoms during infancy or childhood. A follow-up study has shown that symptoms were noted at or soon after birth in 16 patients and between 1 and 16 years of age in 35.

Age at onset of the disease and other clinical features indicate that the patients fall into 3 groups: [1] 10 infants with a neonatal transient type of myasthenia who were born to mothers with the disease, [2] 6 patients with a neonatal persistent (congenital) type whose mothers were unaffected, and [3] 35 patients with a juvenile type of myasthenia gravis whose symptoms began after the first year of life. The clinical features of each group will be described separately.

Neonatal transient myasthenia gravis. Clinical findings in 10 infants are shown in Table 1. All infants were born to mothers with the disease. Of 9 in whom the sex was recorded, 6 were female and 3 were male. Symptoms began some hours after birth in 3 patients, but the exact time of onset was not specified in the remainder.

Symptoms and signs of 5 fully documented cases were as follows: generalized muscular weakness and little spontaneous movement (5); weak Moro response (5); weak suck (5); facial

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TABLE 1

PATIENTS WITH MYASTHENIA GRAVIS OF THE NEONATAL TRANSIENT TYPE

Case number	Sex	Onset	Duration in days	Therapy	Age in years at follow-up	Myasthenia gravis in mother: Duration before pregnancy in years	Myasthenia gravis in mother: Therapy during pregnancy
1 >Sibs	F	Birth	10	Neostigmine	4/12	8	Neostigmine
2	M	Birth	12	Neostigmine	1½	9	Neostigmine
3*	F	Birth	21	None	3½	2	None
4	M	3 days	21	Neostigmine	–	11	Neostigmine
5	M	Birth	?	Neostigmine	3/12	4	None during second and third trimesters
6	F	6 hr.	?	None	5	1½	Neostigmine
7	?	Birth	?	None	1½	¼	None
8	F	6 hr.	18	Neostigmine	2	3	Neostigmine
9	F	Birth	21 (died)	None	–	3	Neostigmine
10	F	Birth	<90	Neostigmine	10	5	Neostigmine

*The diagnoses of neonatal myasthenia in this patient and myasthenia in the mother were not established until 3½ years after delivery.

weakness (3); ptosis (3), unilateral in 1 patient; respiratory weakness (3); and dysphagia (2).

Diagnosis was made at the onset of symptoms in 9 of 10 patients whose mothers were known to have the disease. It was made three and one-half years after delivery in 1 infant, at which time the diagnosis of myasthenia gravis was first established in the mother. Prostigmin therapy was given to 6 infants, and all recovered. Of 4 infants who were not treated, 1 died at the age of 21 days.

Myasthenia gravis had been present in the mothers for three months to eleven years before the pregnancy; 2 received no Prostigmin therapy during the pregnancy, and 1 received none during the second and third trimesters.

Neonatal persistent (congenital) myasthenia gravis. Clinical findings in 6 infants are shown in Table 2. The mothers did not suffer from myasthenia gravis, but 2 cousins of 1 patient and a sister of another were affected. The principal presenting signs were ptosis, weak

TABLE 2

PATIENTS WITH MYASTHENIA GRAVIS OF THE NEONATAL PERSISTENT (CONGENITAL) TYPE

Case number	Sex	Onset	Duration in years	Years elapsed until diagnosis established	Symptoms and signs in neonatal period: Ptosis	Strabismus	Weak suck	Facial weakness	Weak cry	Dysphagia	General weakness	Age in years at reexamination	Symptoms and signs during childhood and later life: Ptosis	Diplopia	External ophthalmoplegia	Chewing weakness	Facial weakness	Dysphagia	Dysphonia	Weakness of limbs	Family history of myasthenia	Drug therapy: Duration in years	Response*	Comments
1	M	Birth	24	22	+	–	–	–	–	–	–	24	+	+	+	+	+	+	+	+	?	2	C	—
2	F	Birth	12	3	+	+	–	+	+	–	+		+	+	+	–	–	–	–	–	–	5	C	Ophthalmoplegia unaffected
3	F	Birth	12	1	+	–	–	–	+	–	+	12	+	+	+	–	–	–	+	–	–	11	B	—
4	F	Birth	20	7	?	–	–	–	+	+	–	20	–	+	+	–	+	+	–	+	+	13	B	Ophthalmoplegia unaffected
5	M	Birth	16	4	–	–	+	–	+	–	+	16	+	+	+	–	+	–	–	–	+	11	B	Paralysis of vertical gaze unrelieved
6	M	Birth	17	4	+	–	–	–	+	–	+	17	+	+	+	–	+	+	–	+	–	12	B	Ophthalmoplegia unaffected

*See text for key.

TABLE 3

PATIENTS WITH MYASTHENIA GRAVIS OF THE JUVENILE TYPE

Case number	Sex	Age at onset (years)	Duration (years)	Years elapsed until diagnosis established	Symptoms and signs: Ptosis	Diplopia	External ophthalmoplegia	Chewing weakness	Facial weakness	Dysphagia	Dysphonia	Weakness of arms	Weakness of legs	Respiratory difficulty	Respirator	Tracheostomy	Drug therapy: Neostigmine	Mestinon	Mytelase	Optimum sustained response	Thymic irradiation: Years after onset	Dose (roentgen) units	Response	Thymectomy: Age (years)	Years after onset	Response	Age (years) at follow-up	Condition at follow-up
1	F	14	1 3/12	3/12	R>L	+	+	−	+	+	+	+	+	+	−	−	+	−	−	C	10/12	1,800	D	15	1	A	23	A
2	F	13	25	6/12	R	+	+	+	+	−	+	+	+	+	−	−	+	−	−	C	8	?	C-D	22	9	B	38	B
3	F	15	5	?	R	+	+	+	+	+	+	+	+	+	+	+	+	+	−	C	2	?	D	17	2	D	20	C
4	F	10	4	<1/12	L	+	+	−	+	−	+	−	−	−	−	−	+	−	−	B							14	B
5	M	9	4½	2/52	+	+	+	−	−	−	−	−	−	−	−	−	+	−	−	A							13	A
6	F	2	1¼	<1/12	R>L	+	+	+	+	+	+	+	+	−	−	−	+	−	−	B	3/12	1,010	A				4½	A
7	M	7	5	4	+	+	+	+	+	+	−	−	−	−	−	−	+	−	−	A							26	A
8	F	11	10	4	−	+	+	+	+	+	+	+	+	−	−	−	+	+	−	B	8	1,500	D	19	8	B	21	B
9	F	12	3	6/12	+	+	−	+	+	+	+	+	+	+	+	−	+	−	−	B	2	?	D	14	2	A	19	A
10	F	14	3	1½	+	−	−	−	+	+	+	−	−	+	−	−	+	−	−	B				16	2	A	19	A
11	M	10	5	1/12	R	+	−	+	+	+	+	−	−	−	−	−	+	−	−	B							15	B
12	F	11	24	9	+	−	−	−	−	−	−	+	+	−	−	−	+	+	−	B				22	11	B	35	B
13	F	16	29	0	+	+	−	+	−	+	+	+	+	−	−	−	+	−	−	B	11	516	D		—		45	B
14	F	7	3	0	+	+	−	+	+	+	+	+	L	−	−	−	+	−	−	B				8	8/12	A	10	A
													>R															
15	M	15	6	3/12	R>L	+	−	+	−	+	+	+	+	−	−	−	+	−	+	B							21	B
16	M	12	18	3	+	+	−	+	−	+	+	R	R	−	−	−	+	−	−	B							31	B
												>L	>L															
17	F	12	1	1	+	+	+	−	+	+	+	+	+	+	+	+	−	+	−	C				13	1	B	13	B
18	F	13	2	6/12	+	+	−	−	+	+	−	+	+	−	−	−	+	−	−	B-C							15	B-C
19	F	12	14	?	−	+	−	+	−	−	−	+	+	−	−	−	+	−	−	B							26	B
20	F	15	7	6/12	+	+	−	+	+	+	+	+	+	−	−	−	+	−	−	B	1½	1,200	D	19	3½	B	22	B
21	F	15	5	2	+	−	−	+	−	−	+	+	+	−	−	−	+	−	−	B				18	3½	A	24	A
22	F	15	5	5/12	+	+	−	+	+	+	+	+	+	+	+	−	+	−	−	C							20	E
23	F	5	1½	0	+	+	+	−	+	−	−	−	−	−	−	−	+	+	+	B							6½	B
24	F	14	18	8/12	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	B-C				32	18	C	32	C
25	F	11	1	0	+	+	+	+	+	+	+	+	+	+	−	−	+	+	−	B-C				12	1½	B	12	B
26	F	11	2	3/12	+	+	−	+	+	+	+	+	+	−	−	−	+	−	−	B-C				13	2	B	13	B
27	F	13	23	3	−	+	+	−	+	+	+	+	+	−	−	−	+	−	−	B							37	B
28	F	16	5	0	L>R	−	+	−	+	−	+	+	+	+	−	−	+	−	−	C	5	2,000	D	21	5	B	21	B
29	F	16	6	4	R	+	+	+	+	+	+	+	+	+	−	−	+	−	−	C	6	1,200	D	22	6	B	22	B
30	F	13	4	1	+	+	−	+	+	−	+	+	+	−	−	−	+	+	−	B-C	4	2,500	C	18	5	C	18	C
31	F	16	6	1½	R>L	+	−	−	+	+	+	+	+	+	−	−	+	−	−	B	4	1,500	?	20	4½	B	22	B
32	F	13	5	4/12	+	−	−	+	+	+	+	+	+	+	−	−	+	−	−	B				15	2	A	18	A
33	F	16	7	<1/12	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	B	7	1,500	D	18	2	B	23	D
34	F	9½	8	3	R>L	+	+	−	+	+	+	+	+	−	−	−	+	+	−	B				13	3½	B	13	B
35	F	8½	3/12	1/12	+	−	−	−	+	−	−	+	+	−	−	−	−	+	−	B							8¼	B

cry, and generalized weakness. In childhood and later life, ptosis and external opthalmoplegia were the most prominent signs; involvement of the bulbar musculature, generalized muscular weakness, and respiratory difficulty were uncommon and of mild degree.

Diagnosis was established late and retrospectively in all patients; the disorder had been misdiagnosed as congenital ptosis in one patient and as cerebral tumor in another.

All patients were treated with Prostigmin or other cholinergic drug therapy; ophthalmoplegia was unrelieved in 4 patients, and complete remission was obtained in no instance. Improvement was objective in 4 patients but only subjective or slight in 2. No patient in this group underwent thymectomy.

The course of the disease was protracted, symptoms were mild but somewhat refractory to therapy, and myasthenic crises did not occur.

Juvenile myasthenia gravis. The clinical findings in 35 children are shown in Table 3 and the ages at onset of symptoms in Figure 1. Symptoms began after 10 years of age in 26 (74%). Girls were affected 6 times more frequently than boys. A family history of myasthenia gravis was not obtained, apart from the occurrence of transient myasthenia in the in fant of 1 patient. A history of ptosis in an uncle and maternal grandmother of 1 patient and of congenital right facial weakness in several members of another family was recorded.

Ptosis, the commonest presenting sign, was unilateral in 5 patients, bilateral but asym-

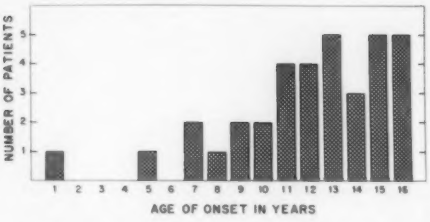

Fig. 1. Age at onset of symptoms in 35 patients with myasthenia gravis of the juvenile type

metric in 6, and bilaterally symmetric in 21. Weakness in the arms and legs was symmetric in 27 and asymmetric in 2 patients. The frequency of occurrence of other symptoms and signs is shown in Table 3. Respiratory difficulty occurred in 43% of patients, and, of these, 40% required tracheostomy and respirator care; it was a postoperative complication of thymectomy in 3 patients and followed irradiation of the thymus in 1.

Symptoms were exacerbated at the time of menses in 8 of 30 female patients, during pregnancy in 3 patients, with infections of the upper respiratory tract in 8, with pyelonephritis in 1, and during emotional upset in 1; 1 patient relapsed after treatment with cortisone and another during sulfonamide therapy for tonsillitis.

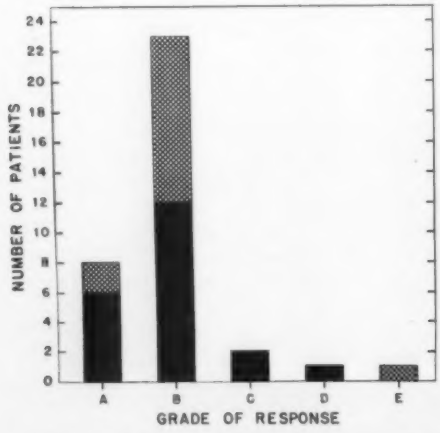

Fig. 2. Results of therapy in 35 patients with myasthenia gravis of the juvenile type. Crosshatching = response to drugs alone. Shaded areas = response to thymectomy and drugs

The diagnosis was established within one year of onset of symptoms in 23 (66%) patients; the longest period that elapsed before diagnosis was nine years. The frequency of incorrect diagnoses was as follows: hysteria (9), hyperthyroidism (2), eye trauma (2), diphtheritic neuritis (1), polyneuritis (1), conjuctivitis (1), respiratory infection (1), and cerebral tumor (1). The erroneous diagnosis of cerebral tumor had led to unneccessary diagnostic neurosurgical procedures.

Associated diseases and the frequency of their occurrence were as follows: thyrotoxicosis (3), atrophy of shoulder girdle muscles with negative muscle biopsy findings (2), depressive psychosis (1), hysteria (1), migraine (1), seizures (1), thoracic scoliosis (1), discoid lupus (1), and late onset of puberty (1).

Therapy consisted of cholinergic drugs, thymectomy, and thymic irradiation. Response to therapy was graded as follows: A = complete remission and drug therapy entirely discontinued; B = good improvement, both objective and subjective, but continuation of drug therapy required in the same or lower dosage; C = slight subjective and/or objective improvement, but large doses of medication necessary; D = no change or worse; and E = death.

Drug therapy. Prostigmin (neostigmine), Mestinon (pyridostigmine bromide), and Mytelase (ambenonium chloride) were administered in 33, 11, and 3 patients respectively; 10 patients received more than one drug. Response to therapy is shown in Figure 2. Of 14 patients who received medical treatment only, 5 were males and 9 were females. An A response was obtained in 2 and a B response in 11; 1 patient died in acute respiratory distress and myasthenic crisis. The treatment and course of the disease in 1 patient who was completely relieved after drug therapy is shown in Figure 3a. In 2 patients, ophthalmoplegia was unrelieved or responded only partially. In 21 patients in whom thymectomy was performed, the response to drug therapy before surgery was graded as B in 11, B regressing to C in 4, and C in 6.

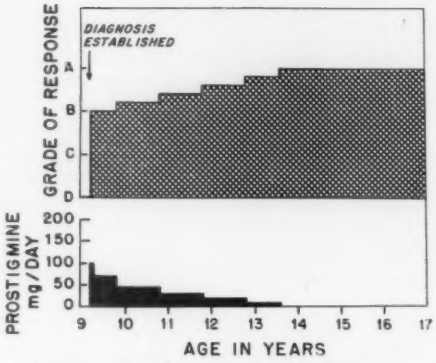

Fig. 3a. Clinical course of patient who responded to drug therapy alone (Case 5)

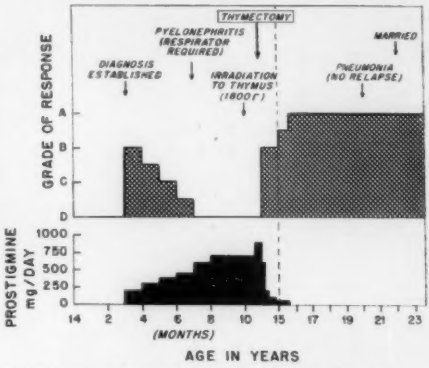

Fig. 3b. Clinical course of patient who responded to thymectomy (Case 1)

Thymectomy was performed in 21 patients, all females. The thymus was irradiated at approximately one to two months preoperatively in 6 patients and at an earlier time in 4. The average age of the patients at the time of operation was 17 years, and the range was 8 to 32 years (Table 3). Symptoms had been present for only eight months in 1 patient and for as long as eighteen years in another; the average duration of symptoms preoperatively was four years.

Response to thymectomy is shown in Figure 2. No patient in this series had a thymoma. Complete, grade A remission in 6 (29%) patients had been maintained at the time of the follow-up for periods of eight, six, five, three, three, and two years, respectively. An improvement in response compared with that to drug therapy preoperatively was observed in 12 patients, no change occurred in 8, and the symptoms were worse after operation in 1. In patients with complete remission, the average duration of symptoms before operation was two years and the average age at operation was 14 years, whereas, in those with a B response to thymectomy, the illness had been present for an average time of five years and the average age at operation was 18 years. The course of the disease in 1 patient with a favorable response to thymectomy and in another whose condition worsened after operation is shown in Figure 3b and c.

A favorable response to thymectomy was not related significantly to previous irradiation of

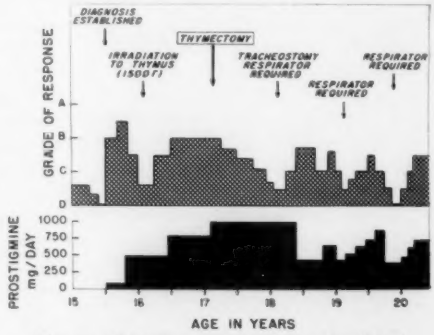

Fig. 3c. Clinical course of patient who failed to respond to thymectomy (Case 3)

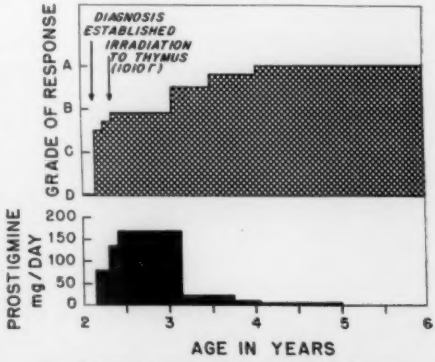

Fig. 3d. Clinical course of patient who responded to thymic irradiation and drug therapy (Case 6). See Table 3 for additional clinical data on each case.

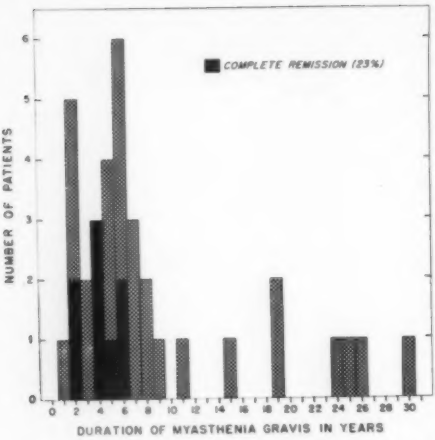

Fig. 4. Duration of disease at time of follow-up in 35 patients with myasthenia gravis of the juvenile type

the thymus. Of 6 patients with an A response, 2 had received irradiation, and, of 12 with a B response, 6 had been irradiated; 2 of the 3 remaining patients who were only slightly relieved or made worse by thymectomy had received irradiation.

Thymic irradiation was performed in 13 patients. In 6, the treatment was administered immediately before operation and its effects could not be evaluated satisfactorily; none showed improvement during a four- to eight-week period of observation. Of the remaining 7 patients, 1 child who was treated at the age of 2¼ years showed a marked grade B remission within one year and a complete grade A remission at the age of 5 years. The treatment and response of this patient are shown in Figure 3d; 1 patient was relieved only slightly, and 5 were not benefitted.

The duration of myasthenia gravis in 35 patients at the time of follow-up is shown in Figure 4. In 8 (23%) patients who had recovered completely, the duration of symptoms was not more than six years.

DISCUSSION

The analysis of 447 patients with myasthenia gravis at the Massachusetts General Hospital has shown that 2% had neonatal myasthenia of the transient type, 1% had neonatal myasthenia which persisted, and 8% were affected with the disease in late infancy or childhood. Thus, 11% had their first symptoms during infancy or childhood. In another large series of cases reported from the Mount Sinai Hospital,[1] the incidence of myasthenia gravis in children was 10%, a figure which agrees closely with our own.

As of 1956, 27 cases of neonatal transient myasthenia had been published since the entity was first recognized in 1935.[2,8] Kibrick[9] reported 4 of these cases and referred to the 2 included in the original report by Viets and Brown.[2] The transitory nature of the disorder suggests the presence of a curare-like substance that passes the placental barrier and is slowly excreted or destroyed by the infant during the neonatal period. That the condition is unrelated to the duration of myasthenia gravis in the mother and to the form of therapy during pregnancy is evident from clinical findings in the 10 patients presented in this report. Maternal disease had been recognized for periods up to eleven years, and 3 mothers had received no drug therapy during the greater part of pregnancy. Geddes and Kidd[10] have reported that thymectomy performed on mothers prior to pregnancy does not prevent the occurrence of disease in the infant. The necessity for early diagnosis and treatment is suggested by 1 fatal case in this series and 3 additional deaths reported in the literature. In 1 instance, the infant died after treatment with Prostigmin,[3] and the possibility of a cholinergic crisis due to overdosage must be taken into consideration.

Some patients have symptoms at birth which persist. This neonatal persistent, or congenital, myasthenia gravis has been classified as an entity distinct from the juvenile type in the present study. Although the evidence is based on a small series of patients, the disease that presents at birth differs from that of late infancy and childhood in the relative mildness of symptoms, protracted course, and resistance to drug therapy. The presence of ptosis and ophthalmoplegia from birth raises the question of an unrelated congenital myopathy, but the improvement with rest and the response of the ptosis to anticholinesterase drugs are strongly in favor of myasthenia gravis. The lack of

response of ophthalmoplegia to drug therapy is common in myasthenia gravis[1] and does not militate against the diagnosis.

In studies of myasthenia gravis in childhood, a satisfactory evaluation of therapy is precluded by the relatively small number of patients with the disease and the lack of controls. In some centers, the majority of patients have been treated medically, whereas, in others, thymectomy has been performed early in the course of the disease. Selection for operation of those patients with more severe symptoms and the lack of conformity in criteria employed for the various degrees of remission render unreliable any comparison of drug and surgical therapies based on evidence available at present. Until patients are allocated for thymectomy at random and a large controlled series is followed, the merits of surgical therapy in juvenile myasthenia gravis cannot be assessed with accuracy. On ethical grounds, a controlled study of this type could be justified only in patients with severe symptoms and if a careful evaluation of present evidence shows no striking difference in the results of surgical and medical therapy.

Keynes[11] reported type A and B remissions in 15 (71%) of 21 children of both sexes who were treated by thymectomy. Those with complete, type A remission who required no drug therapy were not distinguished from the patients with partial, type B remission in whom the dose of medication could be reduced postoperatively but not withdrawn entirely. Of 25 patients reported by Osserman,[1] 15 (60%) responded to medical therapy alone and achieved A and B remissions; a classification similar to that of Keynes was employed.

In our series of 35 patients, 21 underwent thymectomy, and, of these, 18 (86%) showed complete or partial, type A and B remissions. A similar response to medical therapy alone was obtained in 13 (93%) of 14 patients of this series, and the results were comparable with those observed in patients treated surgically. All of the patients in the thymectomy group were female, whereas 5 of the 14 patients treated with medicine alone were males. A more reliable assessment of results based on the percentage of patients with complete remission of symptoms is precluded by the small number of patients for analysis in the present series and by the lack of these data in other published reports.

The response to both medical and surgical treatment in childhood and adolescence appears superior to that in adults. In 100 patients treated by thymectomy and the same number treated medically, Schwab[12] has observed types A and B remissions in 61% and 21%, respectively. The selection of female patients for operation may have contributed to the seemingly good response in this series and in the present group of juvenile patients at the same clinic. A mortality rate of 15% in thymectomized adult patients is not significantly different from that in patients treated medically in other centers.[1,13] Only 1 patient died of the disease in the present series of 35 patients, and she had been treated medically.

The prognosis of myasthenia gravis of childhood and adolescence is generally good, although crises and the need for respirator care may occur in 14% of patients and sudden and sometimes unexplained death is reported occasionally.[14] Complete remission may be expected in 23% of patients and may possibly occur more frequently in response to thymectomy than to medical therapy alone. The value of thymic irradiation in this series of patients could not be assessed satisfactorily, but the complete remission of symptoms which appeared to follow this treatment in 1 child is of interest.

SUMMARY

Of 51 patients with a diagnosis of myasthenia gravis made during infancy or childhood, 10 had transient symptoms in the neonatal period, 6 had symptoms at birth which persisted, and 35 had persistent symptoms which began after the first year of life.

The neonatal transient type of myasthenia gravis occurred in infants whose mothers were affected with the disease; 1 of 4 infants untreated with Prostigmin died.

The neonatal persistent (congenital) type of myasthenia gravis occurred in infants born to unaffected mothers. Symptoms were mild but somewhat refractory to drug therapy, and the course of the disease was protracted.

The juvenile type of myasthenia gravis presented after 10 years of age in 74% of the patients, the majority of whom were girls. Ptosis

and weakness of limbs were the commonest presenting symptoms. The illness was frequently misdiagnosed as hysteria.

Thymectomy was performed in 21 patients; complete remission was obtained in 6 (29%) patients, and objective improvement occurred in 12 (57%). Of 14 patients treated only with cholinergic drugs, 2 (14%) recovered completely and 11 (79%) were objectively improved; 1 patient of this series died of the disease. Complete remission of symptoms followed irradiation of the thymus in 1 young child.

The authors are indebted to Dr. Robert S. Schwab for permission to study the patients from the Myasthenia Gravis Clinic and for his generous advice and encouragement. Thanks are also due to Mrs. Helen Tewksbury and Miss Agnes Masel for their assistance.

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Studies on experimental allergic encephalomyelitis

I. Reduction of electrical threshold of spinal cord in guinea pigs with the disease

Julius Goldberg, Ph.D., and James E. P. Toman, Ph.D.

THE PRODUCTION of experimental allergic encephalomyelitis (EAE) has been facilitated since the introduction of Freund's adjuvant.[1] Numerous species of animals[2–8] have been found to show EAE after injection of homologous or heterologous central nervous system tissue in a water-in-oil emulsion containing mineral oil and killed Mycobacterium tuberculosis. The signs of EAE, both clinical and histopathologic, may vary from animal to animal and from species to species, making quantification of the disease difficult. Percentage of death, percentage of paralysis, histopathology, and combinations of these have been used in the past by various investigators. At present, there is no general agreement as to what criteria should be used in quantifying the disorder. An excellent review of progress of work up until 1957 is given in the symposium edited by Kies and Alvord.[9]

During the course of work on factors promoting or retarding the production of EAE, it was thought desirable to attempt an electrophysiologic quantification of the disorder. This was thought to be of possible value not only for quantification but also because it might shed some light on the altered physiology of the animals during the production of the disease. It was considered important to develop a technic in which measurements could be repeated over a period of weeks with minimal detriment to the animal. Since this precluded surgical intervention such as spinal transection and direct studies on the exposed spinal cord, a technic was designed in which electrical stimulation was applied to the spinal cords of normal and paralyzed (EAE) guinea pigs through the intact vertebral column. The data obtained with the use of this technic, along with certain data secured with the use of standard electroencephalographic and electromyographic technics, form the body of this communication.

METHODS

Production of EAE. Hartley strain male guinea pigs (400 to 500 gm.) were inoculated with 0.2 cc. of an emulsion of homologous spinal cord in Freund's adjuvant, given in 4 closely spaced intradermal injections. Each cubic centimeter of emulsion contained 2.5 mg. wet weight of cord; 2.5 mg. dry weight of heat-killed BCG; 0.425 cc. of bayol F; 0.075 cc. of arlacel A; and 0.5 cc. of saline. Certain animals received in addition 1.5×10^7 Hemophilus pertussis cells incorporated into the emulsion. Control pigs were inoculated in a similar fashion with 1.5×10^7 H. pertussis cells, cord, and adjuvant with BCG. Uninoculated controls were also used. The animals were observed daily and the weights recorded 3 times a week. Since we were interested in the time of appearance, severity, and duration of paralysis in the inoculated animals, the cords and brain were removed only shortly after death of the animal or at the end of the experiment when all remaining animals were sacrificed.

For histologic studies, 40-μ frozen sections

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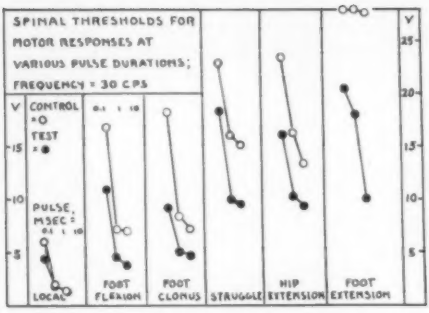


Fig. 1. Thresholds for various motor responses elicited by indirect stimulation of spinal cord in unanesthetized guinea pigs. Open circles, controls; closed circles, previously inoculated with encephalogenic preparation plus adjuvant. Each point represents mean threshold for group of 18 controls and 14 test animals. Pulse durations in each column from left to right are 0.1, 1, and 10 msec. Threshold in relative voltage units

from thoracic, lumbar, and cervical cord, as well as brain stem, were stained for myelin with luxol fast blue and for nuclei and Nissl substance with cresyl violet. The Marchi technic was used for detection of degenerated myelin in selected cord segments.

Indirect cord stimulation. In all, 32 animals were used; 12 had been inoculated with homologous cord in complete adjuvant, and, at the time of testing, 10 were paralyzed. Moreover, 6 pigs from another experiment were used, and, in addition to the cord and complete adjuvant, 1.5×10^7 H. pertussis cells had been inoculated. Of these, 4 were paralyzed at the time of testing. The control groups consisted of 3 animals each, 1 group inoculated with homologous cord, 1 with complete adjuvant, and 1 with 1.5×10^7 H. pertussis cells. In addition, 5 uninoculated guinea pigs were tested. None of the 14 control animals had any signs of paralysis during the experiment.

For cord stimulation, the guinea pig was restrained on a board so that the hind extremities were free. Then, 2 needle electrodes (No. 19, ½ in.) were inserted ⅛ in. apart in the midline, so that the more posterior electrode was at the level of the fourth rib. Bipolar electrical stimulation through the intact vertebral column was done using the following time and frequencies: frequencies of 1, 15, 30, 60, and 240 cycles per second at a constant pulse of 1 msec.; and a frequency of 30 cycles per second and a pulse duration of 0.1, 1, and 10 msec. Stimuli were monitored by cathode ray oscillograph. The minimal current necessary to elicit the various responses was determined (range 0.5 to 30 ma.). The responses noted were [1] local twitch of trunk muscles around the electrode, [2] foot flexion, [3] foot tremor, [4] struggling movements, [5] hip extension, [6] foot extension.

Previous experience with testing of controls by this method under anesthesia or with various depressant drugs showed marked changes and variability in thresholds, so that it was not feasible to utilize anesthesia for the purpose of the present comparison. Similarly, it was not feasible, because of the necessity for repeated study and the nature of the problem, to maintain spinal or decerebrated preparations for the necessary period of the study. It was therefore deemed necessary to carry out the observations in intact, unanesthetized animals. Stimulation external to the vertebral column was chosen, in spite of the theoretic disadvantages, to avoid direct injury to the cord. Excessive and prolonged stimulation was avoided because this in itself might theoretically have produced lasting changes. An arbitrary upper limit of stimulus strength was set to prevent painful responses.

RESULTS

Cord stimulation. Figure 1 shows the results of indirect cord stimulation at a fixed frequency of 30 cycles per second in paralyzed, as compared to nonparalyzed, control animals. Each point shows the mean stimulus value for pulse durations of 0.1, 1, and 10 msec. The connected points form comparable strength-duration curves for comparison of test and controls. The set of curves from left to right are for the various end-point responses listed in order of increasing current required to elicit them. Except for local twitch response, it can be seen that the test values are considerably less than the control values. The differences were found to be quite significant for foot flexion and foot tremor but questionably so for some of the higher threshold end points. Chronaxies determined from curves varied from 0.5 to 2 msec.

with no systemic differences between test and controls or between various types of responses.

Figure 2 shows similar results with the pulse duration held constant at 1 msec. and the frequency varied from 1 to 240 cycles per second. Again, except for local twitch response, thresholds are reduced in the test animals as compared to the controls. In the majority of instances, the difference between comparable points is quite significant at 30 and 60 cycles per second ($P=0.01$), less so at the high or low frequencies. The high threshold end points showed greater variance than did foot flexion or foot tremor.

To obtain a single value expressing cord excitability which would utilize all of the stimulus data, each determination for a given end point in each test in a given animal was divided by the mean threshold value in all animals for that particular test. For each animal, the mean of all such tests was then calculated to give a "threshold index." This method of combining data was thought justifiable because there appeared to be no systematic differences in the data of Figures 1 and 2 other than threshold changes. Mean threshold indexes were then used in comparing animal groups treated differently or for correlation with the degree of paralysis. Figure 3 shows mean threshold indexes plotted against increasing degree of paralysis. The fall in threshold in severely paralyzed animals is quite evident. In the table, the various animal groupings are compared with regard to threshold index. It may be seen from these data that the threshold index is 0.69 for paralyzed animals as compared to 1.24 for nonparalyzed animals ($t=5.1$). In addition, noninoculated animals showed the highest values; controls inoculated with nonparalyticogenic material showed slightly lower values, and the guinea pigs inoculated with encephalogenic material who developed paralysis had the lowest values.

Histopathology. The histologic findings in paralyzed animals were perivascular cuffing, vasodilation, chromatolysis, neuronophagia, gliosis, and motoneuron degeneration. However, the most constant pathologic change was vascular in type. A finding of note was the presence of petechial hemorrhages, usually mediodorsal. The degree of motor neuron pathology was so severe that it was considered out of proportion to the clinical and electrophysiologic data. Examples are given in Figures 4 and 5.

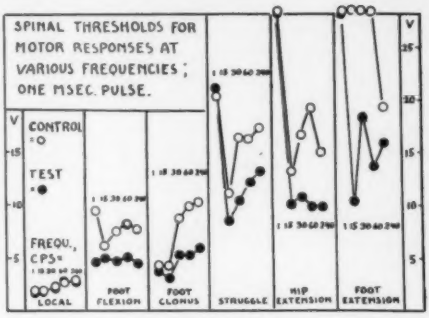


Fig. 2. As in Figure 1, but pulse duration held constant at 1 msec., frequency varied. From left to right in each column, frequencies are 1, 15, 30, 60, and 240 per second.

Incidental findings. In preliminary studies in rabbits, electroencephalographic spontaneous and evoked potentials were observed when implanted epidural needle electrodes were used for stimulation and recording. The electroencephalograms in animals with even severe EAE showed no abnormalities except in those suffering terminal convulsions. In these, the character of the seizure discharges was suggestive of subcortical rather than cortical origin.

In rabbits and guinea pigs, the electromyogram was studied in occasional animals by means of bipolar intramuscular needle electrodes and cathode ray oscillograph recording. Even in severely paralyzed hindquarters, no fibrillations or fasciculations were observed.

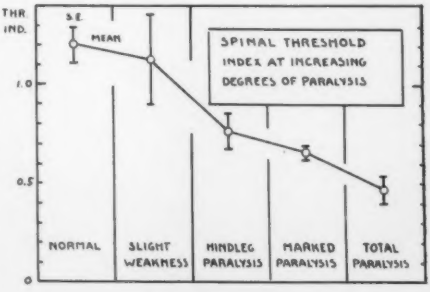


Fig. 3. Threshold index as a function of degree of paralysis. See text for derivation of index.

THRESHOLD INDEXES OF GUINEA PIGS WITH EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS AND CONTROLS

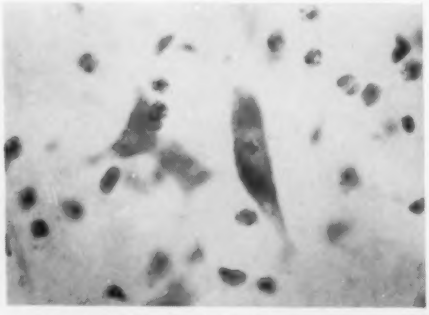
Group	Number of animals	Number paralyzed	Threshold index (mean ± S.E.*) Nonparalyzed	Paralyzed
Inoculated with encephalogenic material	18	14	1.35 ± .14	.69 ± .053
Inoculated controls	9	0	1.03 ± .06	
Uninoculated controls	5	0	1.53 ± .08	
All animals	32	14	1.24 ± .09	.69 ± .053

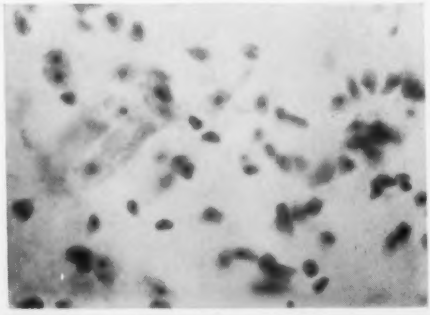
*Standard error

DISCUSSION

Although in recent years much information has been obtained about EAE,[9] the basic pathogenesis is still unclear. Recent findings, if confirmed, would indicate that EAE is much more complex than originally thought. Kies and associates[10] have reported that lipemia is associated with the production of EAE and that the degree of lipemia is proportional to the extent of the disease. Lipton and Freund[7] have pointed out that in guinea pigs a severe weight loss is noted. We have observed that a 40-gm. per day weight loss in 400-gm. guinea pigs is not uncommon, appearing twenty-four hours before the appearance of clinical paralysis. Hurst[11] has also reported that, occasionally, one may observe the development of severe cachexia leading to death rather than the development of the usual neurologic symptoms. In certain animals, moreover, one may observe sudden death without the previous appearance of paralysis. This is especially true during the first ten to twelve days after inoculation, when the animals are first beginning to show reactions.

In addition, the specificity of both the histopathology and the inoculum has been questioned. Tal, Laufer, and Behar[12] have reported that, in the Syrian hamster, injections of adjuvant alone produced inflammatory changes identical with those produced by brain and adjuvant. Demyelinization or clinical signs of central nervous system involvement were not noted. Recently, Svet-Moldavskaya, Svet-Moldavskaya, and Raffkin[13] have reported that prior inoculation of guinea pigs with brain of newborn rabbit with adjuvant is not encephalogenic and, in addition, protects the animals





Figs. 4 *(left)* and 5 *(right)*. Frozen section of lumbar cord stained with luxol fast blue and cresyl violet. Figure 4 shows normal neurons and glial elements in uninoculated guinea pig control. Figure 5 shows equivalent section from inoculated paralyzed animal with marked glial proliferation. A neuron showing typical changes is visible toward top of photograph.

against subsequent EAE when challenged with an encephalogenic inoculum. Of most importance, the brains of these protected animals show the pathomorphologic picture of EAE without demyelinization.

The work of Constantinesco and associates[14] indicates that neural tissue may not be essential for the production of EAE. These authors found that 30% of guinea pigs inoculated with an emulsion of lanolin, paraffin oil, and killed myobacteria had EAE. When brain was incorporated into the inoculum, the number rose to 77%.

Our data indicate that, in the guinea pig, the paralysis induced in EAE is selective, for, in guinea pigs with hindquarters so severely paralyzed as to be useless to the animal, these animals were nevertheless as capable as normal animals of carrying out various movement patterns when stimulated through the intact vertebral column and were in fact hyperexcitable in comparison to the controls. As shown by local twitch thresholds, the motor nerve units to muscle remain essentially normal. Lack of fibrillation also illustrates the integrity of the motor innervation. Lack of fasciculation indicates that the motoneurons are not hyperexcitable to a degree capable of giving spontaneous grouped discharges. The motoneurons, despite their pathologic appearance, are accessible to previously subliminal stimuli from some distance away in the cord but relatively inaccessible to normal reflex pathways or descending paths for integrated locomotion patterns. The most that can be said at this time is that EAE causes a partial and selective disruption of normal cord transmission mechanisms. The apparent hyperexcitability to direct stimulation, as shown by lowered threshold indexes in EAE animals, may well be a "denervation sensitization" phenomenon arising from the partial disruption of local and descending pathways to the motoneurons.

These results would indicate that there is a multiplicity of processes in the production of EAE and that the sequence of events leading to the development of encephalitis may depend upon factors in the host as yet not elucidated.

SUMMARY

The spinal cords of guinea pigs paralyzed from EAE, as well as suitable controls, were electrically stimulated through the intact vertebral column. Thresholds of the elicited responses were lower in paralyzed animals than in controls. The lowering of threshold values correlated with degree of paralysis but did not correlate with degree of histopathology.

The authors are indebted to student fellows H. Scheinman, J. Shapiro, and A. Libanow for technical assistance.

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Temporal dynamometry

Gordon J. Gilbert, M.D.

WITH THE DEVELOPMENT of surgical technics for resection of stenotic or thrombosed atherosclerotic segments of major arteries, it has become of critical importance to delineate precisely the site of vascular disease. Particularly amenable to surgical intervention are discrete lesions involving the carotid vessels extracranially,[1,2] and it has thus been of some consequence to define the syndrome of carotid insufficiency or occlusion. Clinically, the occurrence of multiple transient episodes of hemiparesis, especially when associated with contralateral amaurosis or Horner's syndrome, has frequently been correlated with carotid disease. A blowing or harsh systolic carotid bruit may be present, or carotid pulsation may be diminished. A number of diagnostic procedures have also been used.

Ophthalmodynamometry is performed by observation of the retinal arteries while a known force is progressively applied to the eyeball. One can thus determine the ocular pressure needed to negate the retinal blood pressure and can estimate the blood pressure within the central retinal artery. Should a remarkable unilateral reduction in central retinal artery pressure be discovered, evidence is thereby obtained for an obstructive lesion somewhere between the aorta and the eyeball, that is, in the central retinal, ophthalmic, internal carotid, or common carotid artery.

In certain patients, it is not possible to perform accurate ophthalmodynamometry. Opacities clouding the media or cornea may prevent adequate visualization of the retinal arteries. Atrial fibrillation renders ophthalmodynamometry less accurate, much as it interferes with the exact measurement of the brachial blood pressure. Complications of ophthalmodynamometry are uncommon. In the presence of retinal disease, the transient increase in intraocular pressure may induce retinal detachment. Further, in the period of vascular embarrassment which occurs during the determination of systolic pressure, retinal infarction may ensue. Ophthalmodynamometry should not be performed when central retinal venous or arterial thrombosis is present. Finally, a rare complication of ophthalmodynamometry is subconjunctival hemorrhage[3] as the eye is kicked by the foot of the instrument.

The incidence of complications seems inversely proportional to the experience of the manipulator; of particular import are a smooth increment in applied pressure and the brevity with which systolic pressure is exceeded.

Tilt-table electroencephalography with or without carotid compression can help unravel the vascular dynamics of an insufficiency state[4] by initiating a localized hypotensive cerebral ischemia with concommitant transient electroencephalographic abnormalities. The danger of this procedure is that it may precipitate syncope, focal or generalized seizures, or even cerebral infarction. Carotid compression can produce both local vascular occlusion and a vasodepressor hypotensive reflex; seizures may ensue in over 25% of tilted-and-compressed cases of carotid artery insufficiency.[4]

Cerebral arteriography[5] currently offers the most efficient means for accurate localization of the extracranial carotid lesion; cerebral infarction occasionally complicates arteriography, particularly in older individuals. Maiming of the diseased artery by needle punctures may also induce further thrombus formation, while dissecting aneurysm may occasionally be produced. Arteriography may be undertaken by a number of routes, including femoral catheterization and percutaneous internal carotid, common carotid, and subclavian approaches. Of these, only the first and last may achieve full visualization of the carotid trunks but they are the less frequently used methods. If a simple, rapidly performed, and completely in-

From the Neurological Unit, Boston City Hospital.

nocuous procedure could help define the site of a carotid lesion, it might prove helpful at least in determining the form of angiography to be attempted. Temporal dynamometry seems to meet these criteria.

The theory of temporal dynamometry is simple. If an occlusive lesion is located below the common carotid bifurcation, it may effectively lower blood pressure in both the internal and external carotid arterial trees, while a lesion of the internal carotid artery situated above the common carotid bifurcation should not reduce external carotid artery blood pressure.

METHOD

The branch of the external carotid artery chosen for study was the superficial temporal artery in its course upward just anterior to the external ear. The pulsations of this artery are easily felt by the examiner's index finger placed immediately adjacent to the anterior margin of the ear over its upper half. With a fountain pen, a small X is inscribed on the skin covering the pulsation, symmetrically on the right and left sides. The foot of a standard Bailliart ophthalmodynamometer is placed over the X and pressure gradually applied, the arterial pulsations being palpated at a point just distal to the instrument. The pressure required to occlude the arterial pulsation is directly recorded in grams of water. The entire manipulation is completed within a few seconds and is quite painless. The procedure is repeated until the 3 *lowest* determinations are in the same 5 gm. range. Higher readings are discarded because they represent inaccurate placement of the ophthalmodynamometer foot over the vessel. The same sequence of readings is then performed on the remaining side, and the determinations are compared.

RESULTS

Normal. The table lists the results of temporal dynamometry performed on 24 normal individuals. The pressures in this series ranged from 60 to 120 gm. of water, but the difference between left and right temporal artery readings exceeded 5 gm. in only 2 subjects (10 gm.). The mean difference was 4.2 gm. with a standard deviation of 2.8 gm. Accordingly, a difference between sides of 15 gm., well beyond 3 standard deviation from the mean, was selected as representing the upper limit of normal. As is noted in the table, there was no correlation of the temporal determinations with brachial blood pressure.

RESULTS OF TEMPORAL DYNAMOMETRY IN 24 NORMAL PERSONS

Patient	*Blood pressure (mm. Hg)*	*Temporal dynamometry (gm. H_2O)*	
		Right	*Left*
P.B.	115/ 80	105	105
P.S.	120/ 80	100	105
H.M.	110/ 86	115	120
E.L.	175/110	100	95
E.M.	120/ 70	70	60
R.J.	130/ 90	60	60
S.S.	130/ 80	70	75
Y.T.	130/ 70	75	80
P.M.	100/ 70	70	65
G.M.	130/ 70	105	105
W.W.	130/ 80	105	100
E.S.	130/ 80	90	85
J.E.	110/ 80	100	95
V.E.	110/ 70	70	65
P.R.	120/ 80	90	85
S.R.	130/ 80	115	110
G.U.	110/ 65	110	110
H.S.	120/ 80	105	105
L.C.	140/ 80	95	95
J.A.	120/ 60	90	95
M.L.	110/ 60	115	120
J.J.	130/ 90	90	95
R.M.	120/ 70	85	75
A.A.	100/ 50	55	60

Abnormal. Abnormal temporal dynamometry was found in 2 patients; it was subsequently possible in each case to identify the vascular pathology.

Case 1. A.F., a 51-year-old white man, was admitted to the Neurological Unit of the Boston City Hospital for evaluation of right hemiparesis of seven weeks' duration. He had suffered an anterior myocardial infarction in 1954 and an extension of his infarction one month later. Seven weeks before admission, he suddenly experienced weakness of his right arm, dizziness, and throbbing frontal headache. Over the next twenty-four hours, he noted increasing weakness of the right side of his face and hand, as well as difficulty in pronouncing words clearly. During the following weeks, intermittent headaches associated with transient attacks of blurred vision and dizziness were often related

to postural changes. His speech gradually improved, but, for five weeks before admission, he noticed that his right leg dragged.

On physical examination, the left carotid pulsation was diminished. Blood pressure was 165/100 and pulse 88. Visual acuity was 20/100 uncorrected, bilaterally; funduscopic examination revealed narrowed and slightly tortuous vessels. Right hemiparesis with right-sided hyperreflexia was noted, but the plantar responses were flexor.

Routine laboratory studies were normal; serum cholsterol was 270 mg. per cent. Lumbar puncture obtained clear, colorless fluid under an opening pressure of 100 mm. There were 2 lymphocytes and 11 red blood cells per cubic millimeter. The Pandy test was negative; protein was 35 mg. per cent. Wassermann reaction was negative and the colloidal gold curve flat. Right carotid compression during tilt-table electroencephalography resulted in some irregular slowing in the right hemisphere.

Dynamometry studies. Temporal dynamometry revealed 80 gm. of pressure on the left and 105 gm. on the right. Repeat temporal dynamometry on a later day found similar readings of 85 and 110 gm. Ophthalmodynamometry was performed, the results indicating a pressure of 110/55 mm. Hg for the left central retinal artery and 145/80 mm. Hg on the right.

In view of the temporal dynamometry findings suggesting *common* carotid occlusive disease on the left, low carotid angiography was recommended. Left percutaneous common carotid arteriography revealed complete obstruction of the left internal carotid artery at the bifurcation, with partial occlusion of the external carotid artery at that site.

Comment. Both ophthalmodynamometry and temporal dynamometry revealed lowered pressures on the left side, suggesting that the clinical picture of left cerebral ischemia and infarction was the result of thromboocclusive disease of the left common carotid artery. Arteriography demonstrated an occlusive lesion at the left common carotid bifurcation involving both the left internal and external carotid arteries.

Case 2. L.S., a 56-year-old white man, was admitted on September 15, 1959, to the Neurological Unit of the Boston City Hospital because of left hemiparesis of one month's duration. Five months before admission, a private physician had massaged the patient's right carotid artery because of tachycardia; for two weeks thereafter, he had suffered severe right occipital headache and transient episodes of blurred vision in his right eye. One month later, cervical spine films revealed calcification in the region of the right carotid bifurcation. One month before admission, he began to experience attacks of weakness of the left arm and leg persisting for five to ten minutes and occurring several times a day, with complete recovery after each episode. Several of the attacks were associated with blurred vision and bifrontal headache. Three days before admission, an attack of left hemiparesis was not followed by complete recovery; the patient was confused and expressed himself with difficulty.

On physical examination, the patient was thin and appeared chronically ill. Auricular fibrillation was found, with a pulse rate of 96. Blood pressure was 200/100. Carotid pulsation was absent on the right, and there was a loud systolic bruit that was detected over the left eyeball. The patient was disoriented for time and avoided the right visual field. Moderate left hemiparesis was apparent, as was left-sided hyperreflexia; the plantar response was bilaterally flexor. Over the dorsum of the left hand, there was a slight reduction in pinprick sensation, finger writing, and 2-point discrimination.

Routine laboratory studies were normal; serum cholesterol was 198 mg. per cent. Lumbar puncture obtained clear, slightly xanthochromic fluid under an opening pressure of 70 mm. There were 4,200 red blood cells in the first tube and 4,700 in the third, with 3 lymphocytes per cubic millimeter. Protein was 45 mg. per cent. A tilt-table electroencephalogram showed slowing in the left posterior temporal region.

Dynamometry studies. Temporal dynamometry revealed a pressure of 20 gm. on the right and 80 gm. on the left. Ophthalmodynamometry was performed, the results indicating a pressure of 80/55 mm. Hg for the right central retinal artery and 95/55 mm. Hg on the left.

In view of the clinical picture, temporal dynamometry suggested that an occlusion of the right *common* carotid artery was present. Although an angiographic study of the aortic arch seemed indicated, the patient's deterioration precluded such a study. His left-sided weakness, confusion, and lethargy increased, and his obtundity progressively worsened. At length, he no longer responded to commands and spontaneous movement became confined to the right leg. On October 31, 1959, he became markedly dyspneic and died.

At autopsy, the right common carotid artery was found to be occluded just above its origin from the innominate; the clot extended upward to involve the internal and external carotid arteries. The left common carotid and external carotid arteries were patent, while the left internal carotid artery was only minimally patent due to a recent thrombus. Both vertebral arteries were occluded. Large areas of infarction were present in both cerebral hemispheres, and, in the left posterior parietal area, there was frank liquefaction necrosis. The brain stem and cerebellum were normal.

Comment. By varying the systemic blood pressure, atrial fibrillation interfered with accurate ophthalmodynamometry, the results of

which were inconclusive. However, the pronounced right-sided reduction found with temporal dynamometry suggested that the lesion responsible for the clinical syndrome of right cerebral ischemia was at the common carotid level, while the left common carotid was patent. Although at autopsy there was evidence of extensive atherosclerotic thromboocclusive disease, the left common carotid artery was indeed patent, while the right was totally occluded.

DISCUSSION

The procedure that we call temporal dynamometry offers a simple, painless, and complication-free method for estimating a reduction in external carotid arterial blood flow. The association of an ipsilateral reduction in superficial temporal artery and central retinal artery pressures, with contralateral hemiparesis, suggests a vascular occlusive lesion located at or below the common carotid bifurcation. Angiography can accordingly be chosen so as to include the proximal arterial tree.

How often might temporal dynamometry be useful? In internal carotid thrombosis, 80% of the occlusive lesions are at or just distal to the common carotid bifurcation, while the remaining 20% are intracranial and involve particularly the siphon.[5] Temporal dynamometry may then be employed to help distinguish between operable carotid bifurcation occlusion and inoperable siphon lesion, as illustrated in Case 1. It can also help demonstrate low common carotid thrombosis, as in Case 2. Finally, in cerebrovascular insufficiency situations in which ophthalmodynamometry may be hazardous, contraindicated, or impossible for reasons stated earlier, temporal dynamometry offers a simple and completely innocuous method implicating a lesion at or below the carotid bifurcation.

It need not be emphasized that ophthalmodynamometry alone cannot diagnose carotid occlusion; a unilateral reduction in central retinal artery pressure may be due to occlusion of the innominate, common carotid, internal carotid, ophthalmic, or central retinal artery, and only the presence of other signs of carotid thrombosis would permit that diagnosis to be made. Similarly, a unilateral reduction in superficial temporal arterial pressure could theoretically result from a lesion involving the innominate, common carotid, external carotid, or superficial temporal artery. However, when carotid disease is, on clinical grounds, suspected of contributing to intracranial ischemia or infarction, an ipsilateral reduction on temporal dynamometry would favor an occlusive lesion low in the neck, where surgical intervention may prove feasible.

SUMMARY

A method is described for estimating the external carotid arterial pressure by compression of its superficial temporal branch. The procedure is remarkable in being both theoretically and actually quite free of complications and is simple to perform. The normal range is determined and the abnormal illustrated. Temporal dynamometry has proved useful in helping to identify occlusion of the common carotid artery.

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Electroencephalographic and convulsive responses of patients with brain disease to methetharimide

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METHETHARIMIDE (β, β-methylethylglutarimide), known also as Mikedimide, Megimide, bemegride, and Parlam, has been used as a barbiturate antagonist since 1954.[1-6] It has also been used in electroencephalographic activation[6-11] and is essentially similar in its action to pentylenetetrazol (Metrazol), producing paroxysmal bursts of spikes and slowing[7-11] and grand mal convulsions.[6,10,12] It may be more valuable for this purpose than pentylenetetrazol because the electroencephalographic changes and seizures are induced more gradually and the procedure is easier to control and observe.[7,8,10,11]

Activation studies using pentylenetetrazol have generally been concerned with the study of epilepsy and directed mainly at electroencephalographic changes.[13,10] The work of Ajmone-Marsan and Ralston[13] with a group of patients with chronic epilepsy being evaluated for surgery emphasized that observation of the induced seizure can give data of value in locating an epileptic focus.

The present study was begun to investigate the electroencephalographic and convulsant effects of methetharimide in patients with brain disease with or without epilepsy. Particular attention was given to the effects of the drug in patients with unilateral brain disease. If unilateral disease were to be reflected by an activated electroencephalogram or in focal convulsive phenomena, activation with a convulsant agent might be a valuable tool in the localization of brain disease. This has not been directly investigated in man. Several studies have reported that nonepileptic lesions can cause ipsilateral electroencephalographic changes and contralateral convulsive phenomena.[20,21] In the animal experiments that are reported,[22,23] the lesions have been made with alumina cream and are epileptogenic. They are said to cause focal electroencephalographic changes and contralaterally predominant grand mal seizures. Activation in animals in the presence of other types of brain lesions has not been systematically studied.

PATIENT GROUP

Methetharimide was administered to 63 patients with definite disease of the brain. These patients were divided into 4 groups depending on the site of their disease (Table 1):

- Disease of one hemisphere *(unilateral)*—28 patients had unilateral disease with one or more of the following signs: hemiparesis, hemisensory syndrome, hemianopsia, hemidyskinesia, or focal radiologic findings on arteriogram or pneumoencephalogram.
- Disease of the entire brain *(diffuse)*—19 patients had diffuse disease of the brain with some evidence of disorientation, confusion, decreased recent memory, and decreased intellectual functioning. Most of these patients had pneumoencephalograms that showed diffuse ventricular dilation.
- Definite disease of one hemisphere plus generalized disease of the entire brain *(unilateral and diffuse)*—14 patients had definite clinical or roentgenographic evidence of uni-

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TABLE 1

GENERAL TABULATION OF PATIENTS AND RESULTS

	Total	Type of brain disease present			
		Unilateral	Unilateral and diffuse	Diffuse	Focal bilateral
Patients	63	28	14	10	2
Prior seizures	31	12	7	12	—
Induced focal electroencephalographic changes	21	12	7	1	1
Induced grand mal seizures*	26	13	7	5	1
Induced psychomotor seizures	2	2			
Induced visual sensory seizure	1	1			

*Only first seizure tabulated

lateral disease plus mental changes of an organic type indicating the presence of diffuse disease as well.

• Focal lesions of both hemispheres *(focal bilateral)*—2 patients had hemiparesis of cerebral origin bilaterally.

Unilateral lesions were caused by tumor, vascular disease, trauma, and abscess. Diffuse disease was the result of trauma, alcoholism, infection, toxic diseases, and degenerative disease of the brain. Of the patients, 31 had had prior seizures and were distributed in the 3 main groups.

METHOD

All patients had one or more prior electroencephalograms. A resting electroencephalogram was taken just before the procedure. Under electroencephalographic control, methetharimide was injected intravenously at the approximate rate of 0.5 mg. per second. Photic stimulation at various flash frequencies was presented to 20 of the patients during the procedure. At the beginning of the study, the injection of methetharimide was arbitrarily stopped when paroxysmal electroencephalographic changes appeared or severe myoclonus was produced. Later, it was continued until a grand mal seizure was induced. Seizures were photographed. After induced seizures, approximately half of the patients were given intravenous barbiturates. The patients' comments and responses as well as other clinical manifestations were noted on the electroencephalogram where they occurred.

RESULTS

Electroencephalographic changes. The first electrical change noted was usually an increase in the amplitude of the preexisting rhythms. Then, symmetric, synchronous slowing and spiking commonly occurred. However, in 12 of the 28 patients with unilateral brain disease, the earliest electroencephalographic changes were focal—either the development of a focus where none had existed before or the accentuation of preexisting focal abnormalities. These focal changes were generally 2- to 6-per-second focal slowing or focal spikes and spike waves and were not specific in any way other than their appearance over the diseased hemisphere. Of the 14 patients with both unilateral and diffuse disease, 7 had the same results. The earliest abnormality appeared over the side of the unilateral brain disease. In contrast, only 1 of the 19 patients with diffuse disease had early focal changes. The other 18 had symmetric and diffuse changes; 4 normal patients who were tested separately also showed only diffuse electroencephalographic changes.

In the immediate preictal state, the electroencephalogram was symmetric in most cases. A few patients with unilateral brain disease had more slowing of higher amplitude over the side of disease. In all but one case, this had appeared earlier in the activation. A patient with a visual sensory seizure in the left homonymous visual field had an ictal slow wave discharge in the right occipital area. During the grand mal seizures, the electro-

encephalograms were usually obscured by movement and muscle artifact. In 2 patients, a postictal slow wave focus appeared over the side of the unilateral disease. Generally, however, the postictal records were diffusely slow with no focal findings.

Thresholds. The amount of methetharimide needed to produce the first electroencephalographic abnormality varied from 10 to 205 mg. Most patients received a total of 100 to 450 mg. However, one patient received 915 mg. without having a typical grand mal seizure. This wide range in dosage made it impossible to predict what the threshold would be in the individual patient. Several patients with seizures and a few others with severe brain disease responded after 10 to 20 mg. of the drug. Others were very resistant to its action. This is similar to the finding of variable threshold levels with pentylenetetrazol.[15,16,19,24,25]

Photic stimulation. The reaction to photic stimulation was markedly increased by methetharimide. Flicker was usually most effective at 15 cps. If it caused occipital following in the resting record, it would cause spikes and spike waves after methetharimide. Some patients who had no following in the resting record developed evoked responses proceeding to spikes and myoclonus. Others continued to be unresponsive. When multiple spikes appeared, they were often associated with myoclonus, frequently occurring before any other electroencephalographic change.

Symptoms. The patients' subjective symptoms during the procedure were generally mild. Some apprehension occurred in 14 patients, most of whom had been anxious before the procedure began; 9 patients complained of dizziness, 3 of tiredness and drowsiness, 3 of nausea and a bad taste in the mouth, and 2 of feeling as if they were about to fall, though lying flat on a stretcher. In 1 of these patients, the sudden sensation of falling was reproduced at a second separate testing. Both times, this appeared after the injection of approximately 150 mg. of methetharimide with no associated electroencephalographic changes. Eyelid flickering was not often seen, although it is reported to be common after rapid injection.[9,26] Postictal confusion was common after seizures. No significant morbidity and no mortality resulted from the procedure.

Myoclonus was usually the first clinical seizure activity that occurred during the injection of the drug. It would appear without warning, often correlated with electroencephalographic spike activity. The first limb involvement was as often ipsilateral as contralateral in the patients with unilateral brain disease. As more methetharimide was injected, the myoclonus became generalized. Photic stimulation markedly increased the amount and extent of the myoclonus.

Persistent one-sided clonic activity developed in 7 patients with unilateral brain disease during the injection of methetharimide. This focal clonus was contralateral to the brain disease in 6 patients and ipsilateral in 1. It did not develop in patients with diffuse brain disease.

Seizures. Generalized seizures were produced in 29 patients on 36 different occasions; 26 had grand mal seizures, 2 had psychomotor seizures, and 1 had a visual sensory seizure. At a second testing, 5 patients had grand mal seizures, and 1 patient had a third induced grand mal. These seizures were stereotyped tonic-clonic convulsions and lasted about sixty seconds. During the tonic phase, the head and eyes often turned, the body would stiffen, and various slow movements of the body were noted, including flexion or extension of the arms, flexion or extension of the legs, and torsion of the trunk. Arm movement was the most common of these. If these movements predominantly involved one side of the body, the tonic phase was called "predominantly one-sided." If both sides were involved but the positioning of body parts was different, the tonic phase was classified as "bilateral asymmetric." Finally, if the positioning of both body sides was equal, the tonic phase was called "bilateral symmetric."

Head turning and conjugate deviation of the eyes were found to be as often ipsilateral as contralateral in patients with unilateral lesions. They also occurred in 4 of 5 patients with diffuse disease. In 4 of 5 patients who had a second drug-induced seizure, the head and eye turning was not in the same direction as during the first seizure. The head either failed to deviate or deviated when it had not done so before. In 1 patient with 3 seizures, the first and third were accompanied by head

TABLE 2

ANALYSIS OF CONVULSIVE PHENOMENA

	Total	Type of brain disease present: Unilateral	Unilateral and diffuse	Diffuse	Focal bilateral
Early unilateral myoclonus	16	9—5 c 4 i	3—1 c 2 i	3	1
Focal clonus	7	4—4 c	3—2 c 1 i		
Head and eye turning	17	9—5 c 4 i	4—3 c 1 i	4	
Absence of head and eye turning	9	4	3	1	1
Predominantly one-sided tonic body movements	14	8—7 c 1 i	5—4 c 1 i	1	
Predominantly bilateral tonic body movements	12	5—1 s 4 a	2—2 s	4—3 s 1 a	1—1s

c—contralateral to side of brain lesion
i—ipsilateral to side of brain lesion
s—symmetric body positioning
a—asymmetric body positioning

and eye deviation to the left and the second to the right. A patient had turning of his head to the right during an observed spontaneous seizure and to the left during a drug-induced seizure. Head and eye turning was consistently contra- or ipsilateral and therefore not accurate in lateralizing cerebral pathology.

Predominantly one-sided tonic body movements occurred in 14 patients, (Table 2), 8 with unilateral brain disease and 5 who had both unilateral and diffuse disease. These movements were contralateral to the lesion in 11 and ipsilateral in 2. In addition, 1 patient with diffuse brain disease had predominantly one-sided movements. Asymmetric but bilateral body movements developed in 4 of the patients with unilateral brain disease and in 1 patient with diffuse disease. Symmetric bilateral body movements were present in 1 patient with unilateral disease, 2 with unilateral and diffuse disease, and 3 with diffuse disease. Thus, in the tonic phase, patients with unilateral brain disease showed a greater tendency to predominantly one-sided body movements (most often contralateral to the lesion) or to asymmetric movements than to generalized movements. Diffuse disease seemed to cause mostly generalized body movements in those patients of this group who had an induced convulsion.

During the clonic phase, all patients had generalized alternating flexion and extension of the arms and legs. No asymmetry was seen. Apnea that developed during the seizures would abate toward the end of the clonic phase. Most patients did not urinate or defecate. Severe sweating was noted in a few patients. After about thirty seconds, the patients relaxed and were comatose or stuporous for a variable length of time. After the seizure, few focal signs were noted, although several times postictal weakness appeared or was more marked than before. This was always on the side of the body opposite a unilateral lesion.

Incidence of focal signs. The majority of patients with brain disease on only one side, 21 of 28, exhibited either focal electroencephalographic changes, focal clonus, or predominantly one-sided body movements in the tonic phase of the induced grand mal seizure (Table 3). However, 15 of these 28 patients were not given seizures and presumably might have had other focal signs during a convulsion. More than one focal sign occurred in 3 patients, and in only 1 of the 28 was the electroencephalogram diffuse, focal clonus absent, and the grand mal seizure generalized. Of 14 patients with both unilateral and diffuse disease, 12 had focal signs, with more than one of these signs in only 3. In contrast, only 1 of the 19 patients with diffuse disease had early focal electroencephalographic changes, none had focal clonus, and 1 had predominantly one-sided tonic body movement. Since only 5 of these patients had induced grand mal seizures, it is possible that other focal manifestations might have occurred.

It appears that, if a unilateral lesion exists, there is a good chance that lateralizing signs will appear during activation. If no focal electroencephalographic signs or focal clonus appear, frequently, the grand mal seizure will give focal signs not previously present. This was true in 8 of the 13 patients with unilateral brain disease who had one-sided tonic movements although their electroencephalograms were diffuse and focal clonus had not appeared. We do not have anatomic studies that might help explain the ipsilateral nature of the focal clonus in 1 patient, the ipsilateral tonic movements in 2 patients with unilateral brain disease, and the one-sided tonic predominance in 1 patient with diffuse disease.

DISCUSSION

On the basis of these results, it is likely that methetharimide can be of value in diagnosing unilateral brain disease. If a unilateral lesion is present, it may be activated to cause focal electroencephalographic changes, focal clonus, predominantly one-sided tonic body movements during induced grand mal seizures, or postictal weakness. It would appear that relatively few focal lesions do not cause some focal reaction. However, false lateralizations do occur in patients with unilateral disease and in others with diffuse disease.

Other studies seem to support these findings.. During activation, two of the signs which Ajmone-Marsan and Ralston[13] considered as reliable indicators of focal brain disease were present in our series: focal clonus and one-sided tonic body movements. These signs were correctly lateralizing in about the same proportion as in their series.

Ajmone-Marsan and Ralston also listed preictal aphasia, unilateral tonic facial contraction, and head turning as localizing signs. We saw only one case of the first and did not especially note the incidence of the second. Head movements were not reliable above a chance level. In our series, there were fewer automatisms that were separate from the grand mal attacks and fewer psychomotor seizures. This is probably the result of the differences between the groups; the Ajmone-Marsan and Ralston group contained only epileptic patients, many of whom had temporal lobe seizures. Signs that they considered to be unreliable were early one-sided myoclonic jerking, eye movements, and asymmetric grand mal seizures. Our findings were in agreement with this.

Further confirmation of the focal effect of activation was obtained by Werman and associates.[21] Using intracarotid methetharimide, they produced focal electroencephalographic changes and focal convulsions in patients with

TABLE 3

OCCURRENCE OF FOCAL SIGNS

	Type of brain disease present			
	Total (unilateral)*	*Unilateral*	*Unilateral and diffuse*	*Diffuse*
Total focal signs	33	21	12	2
Focal electroencephalographic signs	19	12	7	1
Falsely lateralizing electroencephalographic signs	—	—	—	1
Focal clonus	7	4	3	—
Falsely lateralizing focal clonus	1	—	1	—
Predominantly one-sided tonic body movements	13	8	5	1
Falsely lateralizing one-sided tonic body movements	2	1	1	1
Patients with more than one focal sign	6	3	3	—
Patients with no focal electroencephalogram, no focal clonus, who had one-sided tonic body movements	8	6	2	1

*Combination of unilateral group and unilateral and diffuse group

unilateral brain disease. In contrast, injections of pentylenetetrazol in patients with no unilateral brain disease produced bilateral synchronous electroencephalographic responses.[27] Likewise, Margerison[9] noted in his study of the reaction of 10 normal individuals to methetharimide that "the main point of interest in the electroencephalographic findings is that while paroxysmal discharges of what might be termed an epileptic type were seen, focal cortical discharges from some discrete area of the brain never occurred."

The site and mechanism of methetharimide action has not yet been firmly established. Promising suggestions have been advanced concerning its chemical action[28] and its action on cerebral blood vessels,[29] but the reason why cells on the damaged side might react first is still unknown. In our study, there was no relationship between the nature of a particular lesion and the development of a focus. The presence of damaged cells seemed to be the important factor in determining focal reactions.

Work with pentylenetetrazol has indicated that it increases the intra- and subcortical elaboration of impulses,[30–32] which may account for the marked visual-motor facilitation seen in photomyoclonus.[17,30] This response is not necessarily dependent on the presence of the cortex.[33] It is possible that methetharimide acts in a similar fashion to produce these same clinical effects.

SUMMARY

A group of 63 patients with disease of the brain was investigated with methetharimide (β, β-methylethylglutarimide), an activating and convulsant agent. Particular attention was paid to focal electroencephalographic changes and focal aspects of induced seizures. Clinical effects of the drug were mild. No mortality and no significant morbidity occurred.

General electroencephalographic activation of slowing and spikes was commonly produced. Response to visual (photic) stimulation was markedly increased by the drug, and flicker often produced myoclonus. Early focal electroencephalographic changes on the side of the lesion were produced in 12 of 28 patients with unilateral brain disease and in 7 of 14 patients with both unilateral and diffuse brain disease. In contrast, 18 of 19 patients with diffuse brain disease had only diffuse electroencephalographic changes.

Grand mal seizures were induced 33 times in 26 patients; 2 patients had psychomotor seizures, and 1 had a focal visual sensory seizure. In the grand mal seizures, head and eye turning was commonly seen but could not be correlated with unilateral brain disease. On the other hand, tonic one-sided body movements, mostly of the arms, occurred in 13 of 20 patients with unilateral brain disease. In 11 of these 13, they were contralateral to the diseased side and were ipsilateral in 2. Focal clonus appeared only in patients with unilateral brain disease and was contralateral in 6 of 7. Myoclonus had no lateralizing value. Postictal weakness was a reliable sign but did not occur frequently. Patients who had electroencephalographic foci or focal clonus were generally not those who had focal signs during induced grand mal seizures.

Methetharimide appears to be safe for electroencephalographic activation and has been valuable for the study of induced seizures in patients with brain disease. Although, errors in lateralization have been noted, activation appears to be a useful supplement in diagnosing unilateral brain disease.

Methetharimide for this study was supplied as Mikedimide by the Pan-Ray Corporation, Englewood, N. J.

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Treatment of gliomas of the third ventricle and pinealomas

With special reference to the value of radiotherapy

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DIRECT SURGICAL ATTACK upon tumors of the pineal region and the third ventricle carries a very high mortality rate, whereas radiotherapy accompanied by surgical relief of obstructive hydrocephalus, when necessary, circumvents the mortality associated with surgical intervention and results in many long-term useful survivals. Because these facts are not sufficiently well recognized, we are presenting the case material of the Neurological Institute to emphasize this more successful mode of treatment.

PRIOR INVESTIGATION

This high mortality, particularly of the posterior transcallosal approach to the pineal and posterior third of the third ventricle, has been pointed out by many neurosurgeons. Cushing[1] writes, "I have never succeeded in exposing a pineal tumor sufficiently well to justify an attempt to remove it." Dandy's figures[2] are the best of any—20% mortality in series of 20—but even he states that pineal tumors "are perhaps the most dangerous of all intracranial tumors to attack surgically." The operative mortality from Olivecrona's clinic[3] was 58.8% in a group of 51 patients in whom radical or partial extirpation of pineal tumor was carried out. No good figures are available on the operative mortality of tumors of the anterior two-thirds of the third ventricle. We exclude colloid cysts because they are readily diagnosed and easily removed. The ones we have in mind must be culled from other groupings and do have a high mortality.[4–6]

Such discouraging results have led others besides ourselves to turn to a form of treatment unaccompanied by this high mortality rate. Of these, Horrax[7] has taken the lead in advocating the treatment of pinealomas by irradiation accompanied by subtemporal decompression. Of 13 cases verified by operation, only 3 (1 of whom also received radiotherapy) were alive five and one-half to twelve years after complete removal. On the other hand, 7 out of 9 of his patients were alive and well (except for 2 with diabetes inspidus) two to seventeen years after decompression and radiotherapy and 1 for ten years after radiotherapy alone.

Ward and Spurling[8] advocate subtemporal decompression to relieve pressure and to save vision followed by the radiation therapy; 14 patients were treated in this manner, 8 of whom failed to respond and were found to have either cysts or unresponsive malignant gliomas at subsequent operation. The remaining 6, including 3 with probable pineal tumors, survived up to sixteen years.

In a report on tumors of the posterior third of the third ventricle, Rand and Lemmen[9] state that, because of a 70% mortality in 17 cases operated upon, they turned to conservative therapy, that is, a shunting procedure (third ventriculostomy in 9 cases and ventriculocisternostomy in 3) followed by radiotherapy. Of these 12 patients, 9 were alive two to ten years after treatment.

Kahn[10] states in his textbook on neurosurgery: "It is generally agreed, however, that

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TABLE 1

LESIONS MISDIAGNOSED BY AIR STUDIES

Other lesions diagnosed as third ventricle neoplasms (22 of 106 cases)

Colloid cyst	6
Epidermoid cyst	2
Epidermoid (pearly) tumor	1
Dermoid cyst	1
Craniopharyngioma	3
Chromophobe pituitary adenoma	1
Astrocytoma secondarily invading	2
Glioblastoma secondarily invading	2
Hemangioblastoma of cerebellum	1
Medulloblastoma of cerebellum secondarily invading	1
Congenital aneurysm of vein of Galen	1
No tumor found at operation	1

Other lesions diagnosed as pineal neoplasms (5 of 106 cases)

Extensive astrocytoma deforming posterior third of third ventricle	3
Medulloblastoma metastatic to region of pineal and cisterna ambiens	2

with present day methods such tumors [posterior third ventricle] cannot be totally removed or even biopsied without forbidding mortality." He recommends lamina terminalis puncture and radiotherapy. Should there be a problem in differential diagnosis between such a tumor and posterior fossa tumor, he advocates exploration of the posterior fossa and the use of ventriculocisternostomy if the exploration is negative. Ennuyer[11] from the Curie Institute advocates a bypass procedure, when necessary, followed by radiotherapy and radiotherapy alone when ventricular dilation is not marked. Fincher, Strewler, and Swanson[12] reviewed their experiences with shunting procedures. Many of their cases too received radiotherapy.

MATERIAL

The material for this study has been collected by reviewing all of the cases of third ventricle or pineal tumors cross-indexed in both the diagnostic and therapeutic files of the Department of Radiology and all cases filed in the hospital record department with the diagnosis of one of these lesions on discharge from the hospital. A few charts were not available to us. Except for these, we think no case in which the diagnosis was seriously considered has escaped us. These total 106. Since the diagnosis of these lesions depends so heavily upon air studies and since we advocate treatment of these tumors without pathologic verification, it seems proper to review the possibility of error in such a method.

Table 1 lists the cases in which a dignosis of third ventricle tumor was made and subsequently shown to be in error, either at operation or at autopsy; 6 of these were colloid cysts, 5 being from the period before 1935. Since that time, these cysts have been correctly diagnosed by air studies, except 1 that was unusual in its location within the third ventricle. This fact caused it to be missed at operation also and be found only at autopsy. The astrocytomas that secondarily invade the third ventricle usually show evidence of extensive tumor elsewhere by air study. The 4 listed here, however, did not have such evidence. The other confusing tumors are few in number. In craniopharyngiomas and pituitary tumors, the use of pneumoencephalography or angiography after ventriculography will frequently distinguish between an intraventricular mass and a sellar or suprasellar mass invaginating the floor of the third ventricle. If this does not solve the dilemma, surgical exploration of the base of the brain may be carried out. This does not carry the high mortality of the direct approach to third ventricle tumor. Similarly, posterior fossa exploration should be performed if the possibility of cerebellar tumor distorting the third ventricle cannot otherwise be ruled out. If the posterior fossa is found free of disease, the Torkildsen procedure can be done at once.

Epidermoid and dermoid cysts present the most difficult problem. These may be intraventricular and yet not as characteristic in appearance as colloid cysts. Patients with these will, under our method of treatment, be considered as having third ventricle tumors, improved by relief of obstruction yet unresponsive to irradiation. Subsequent direct surgical removal may or may not be necessary because these lesions are so slow in enlarging. Torkildsen[13] himself had several long-term survivors after shunting alone without irradiation. Some of his patients may well have had these lesions.

Table 1 also shows the nature of the lesions which were diagnosed as pineal neoplasms but which were later proven to be something else;

3 extensive astrocytomas were called pinealomas because their only manifestations on air study were deformities of the posterior third of the third ventricle. The problem of misdiagnosis of medulloblastomas, as happened in 2 instances, is of great importance because the plan of radiation therapy would be different. This mistake is made when the symptomatology is atypical and metastasis is to the pineal region, fortunately a rare combination.

Table 2 shows the opposite situation; 8 of 106 cases were of third ventricle tumors diagnosed by air study as being some other lesion; however, the diagnosis that was made led to exploration and establishment of the correct diagnosis. Indeed, our policy is that, if there is any doubt, the need for exploration should be emphasized despite the operative risk.

The material with which we are primarily concerned, therefore, consists of 79 cases: 22 proved tumors of the third ventricle, 15 proved pineal tumors, and 42 lesions diagnosed by air study and treated without prior or subsequent verification. Of this last group, 21 are considered to be pineal tumors because the air study showed the tumor to be in the posterior third of the third ventricle. The rest, or 21 tumors, were considered to be third ventricle gliomas. Of the glioma patients, 24 were males with an average age of 25 years and 19 were females with an average age of 23 years. Of the pineal patients, 26 were males whose average age was 19; only 10 were females, and their average age was 26.

The gliomas of the third ventricle must, of course, arise from the structures that either line or bound the third ventricle. Their bulk is almost entirely within the third ventricle, although some may have limited local extension. The types of gliomas in those cases in which a tissue diagnosis was made are given in Table 3. We have also included 3 rare tumors found within the third ventricle, not gliomas but ones that might respond to radiotherapy. The pineal tumors are also given in Table 3. The classification of these tumors is a complex matter of great interest.[3,14] The nomenclature is that used in our Department of Neuropathology at the time of the examination of the various specimens. We have included 5 cases of ectopic pineal tumors for the sake of completeness.

TABLE 2

LESIONS MISDIAGNOSED BY AIR STUDY
(8 of 106 Cases)

Third ventricle lesions misdiagnosed as:	
Colloid cyst	4
Hypothalamic tumor	1
Suprasellar tumor	1
Brain stem tumor	1
Posterior fossa tumor	1
No pineal tumor was misdiagosed.	

METHOD OF TREATMENT

The anatomic location of these tumors makes their treatment a matter of special consideration. The presenting symptoms and the immediate threat to life are due almost always to obstruction of the outflow tract of the cerebrospinal fluid at the level of the foramina of Monro, the third ventricle itself, or the aqueduct of Sylvius. Surgical relief of this obstructive hydrocephalus is the immediate goal of treatment. Radical or even partial removal of the tumor would accomplish this, but the anatomic location, so near the vital centers of the brain, accounts for the excessive mortality rate previously mentioned. On the other hand, the location of these tumors, either adjacent to or lying within a cavity of the brain, may be the explanation for relatively good response to irradiation. The availability of an enlarging

TABLE 3

PROVED LESIONS

Third ventricle neoplasms		
Astrocytoma		13
Ependymoma		4
Mixed astrocytoma and oligodendroglioma		1
Mixed astrocytoma and ganglioneuroma		1
Ganglioneuroma		1
Papilloma of choroid plexus		1
Congenital epidermal tumor (nonameloblastic) of Rathke pouch origin entirely within third ventricle		1
		22
Pineal neoplasms		
Pinealoma		5
Teratoma of pineal		2
Atypical teratoma of pineal		1
Oligodendroglioma	Probably atypical teratomas of the pineal	1
Ependymoma		1
Pinealoma (ectopic)		4
Atypical teratoma of Pineal (ectopic)		1
		15

space in which to grow seems to curb the deep infiltration of many of these tumors.

Treatment of these tumors at the Neurological Institute has varied over the years. In the early years, direct exploration for verification and possible removal was frequently attempted. These cases contributed the high mortality that led to our present mode of treatment. Of the short-circuiting procedures used, many were by the method described by Stookey and Scarff[15] and many by the Torkildsen ventriculocisternostomy.[16] Sometimes, these have been combined with splitting of the tentorium to provide local decompression. Ventriculoureteral anastomoses have been used when the Torkildsen has not functioned well.

Radiotherapy technic as formulated by Dyke[17] was carried out for all but the more recent cases. This consisted of 3 short courses of irradiation spaced several weeks apart; 1 case was treated by a massive dose given to the exposed pineal tumor in the operating room. Since mid-1952, a single definitive course of therapy with a tumor dose of 4,000 r in four weeks or 5,000 r in six weeks has been our goal. Children are treated by our modification of Richmond's schedule,[18] that is, 50% of the adult dose for infants of 1 year over the same period of time, 75% at 5 years, or the adult dose by 8 years. We now usually use 4 ports: 2 opposing lateral ones, a vertex, and a high occipital port. These vary in size depending upon the size of the lesion, the lateral ports usually being 6 × 6 to 8 × 8 cm. If a shunt has been performed and is working properly, the daily dose can be raised rather rapidly so that by five days a tumor dose of 165 r, the usual daily dose for the duration of the treatment, is reached. If no shunt has been performed, initial daily dosage is much less; the dose is increased slowly until the usual amount is reached on the eighth or ninth day. All of our patients were treated with conventional voltage, at least initially. Many, particularly those treated by the multiple series method, have been retreated as the need arose.

Some authors advocate the treatment of pinealomas in the same fashion as medulloblastomas, including treatment of the cord. We do not agree with this, preferring to give a higher dose to the primary tumor than might be otherwise possible. Because only 2 of 36 patients with pinealomas have had spinal cord metastasis, it seems undesirable to subject all patients to extensive and prolonged treatment.

RESULTS OF TREATMENT

Table 4 shows how these cases were managed and what the outcome has been. Only 2 of the 79 were lost to follow-up. These are considered dead as of the time of the last contact and are indicated by parentheses. Of the 4 patients who had total extirpation of the tumor, 3 died. The 1 now living after nineteen years had an oligodendroglioma, probably a form of teratoma of the pineal, removed in toto. This is the only patient in the series who, having survived surgery, did not receive radiotherapy; 9 patients had less extensive surgery and died. Of 10 of those who survived surgery and received adequate radiotherapy, 6 are now living with very long survivals; 1 of the 4 who did not survive should be described in greater detail. At operation, by means of a lateral ventricle approach, tumor was seen in the third ventricle arising from its floor and 1 wall. This was partially removed and proved to be an astrocytoma. The patient received extensive irradiation. She died four years later of acute peritonitis. At autopsy, no gross tumor could be seen within the brain. Microscopy showed atypical cells in the wall of the third ventricle, presumably radiation-modified tumor cells.

We have used the term inadequate radiotherapy to mean those instances when patients received 2 or less of the usual series of 3 courses of radiotherapy under the old plan or 2,500 r tumor dose or less under our current plan. In general, these patients died before therapy could be completed.

The shunting procedure itself was the cause of 2 deaths. All the survivors of this surgical procedure were treated by irradiation. Again, in general, those who received adequate treatment were those who survived long enough to complete the planned course. However, 1 patient refused further treatment after 2,000 r tumor dose, survived almost five years, and then died of her tumor, as was demonstrated at autopsy. Another patient died during his second radiation treatment of what appeared to be myocardial infarction or pulmonary embolus. This is counted as a failure of irradiation rather than an operative death from

TABLE 4

FORM OF TREATMENT AND RESULTS

	Total	*Died*	*Interval before death*	*Living*	*Survival time (years)*
Direct surgical approach only					
Total excision					
Third ventricle	3	3	0, 2 days, 2 days		
Pineal	1			1	19
Partial removal	None				
Biopsy					
Third ventricle	6	6	0, 1 day, 1 day, 2 days, 3 days, 3 days		
Pineal	None				
Attempted exploration					
Third ventricle	2	2	0, 1 day		
Pineal	1	1	(8 days)¶		
Direct surgical approach plus radiotherapy					
Partial removal plus adequate radiotherapy					
Third ventricle	6	2	6 mo., 4 yr.*	4	3¾, 16, 16, 17
Pineal	4	2	5 yr.,† 6 yr.†	2	15, 15
Partial removal plus inadequate radiotherapy					
Third ventricle	1			1	3
Pineal	None				
Biopsy plus adequate radiotherapy	None				
Biopsy plus inadequate radiotherapy					
Third ventricle	1			1	6
Pineal	1	1	3 mo.		
Biopsy plus radiotherapy in operating room					
Third ventricle	None				
Pineal	1	1	2 mo.		
Shunting procedures only					
Third ventricle	1	1	2 days		
Pineal	1	1	1 day		
Shunting procedures plus radiotherapy					
Shunt plus adequate radiotherapy					
Third ventricle	15	3	3 mo., 2½ yr., 6 yr.	12	1, 1, 2, 2, 4½, 5, 5, 6, 6, 6,‡ 7,‡ 15
Pineal	11	4	3 mo., 6 mo., 2 yr., 3 yr.§	7	2, 2, 2, 2½, 4, 4, 7
Shunt plus inadequate radiotherapy					
Third ventricle	2	2	1½ mo.,§ 2 mo.		
Pineal	7	7	7 days, 1 mo.,‡ 2 mo., 2½ mo., 2½ mo., 1½ yr., 4⅝ yr.		
Radiotherapy only					
Adequate radiotherapy					
Third ventricle	6	1	(6 yr.)‖¶	5	1, 2, 3, 3½, 6
Pineal	4	2	7 mo., 1 yr.	2	8, 13
Inadequate radiotherapy	None				
Ectopic pinealomas					
Partial removal plus adequate radiotherapy	1			1	8
Partial removal plus inadequate radiotherapy	1	1	4 mo.		
Biopsy plus adequate radiotherapy	2			2	4, 12
Biopsy plus inadequate radiotherapy	None				
No treatment	1	1	5 days		

*Died of intercurrent disease and autopsied
†Died of metastasis to cord
‡Also biopsied
§Also subtotally removed
‖Subtemporal decompression also
¶Lost to follow-up

TABLE 5. MORTALITY AND SURVIVAL RATES

*Operative mortalities**	Total	Deaths	Per cent
Direct surgical approach	32	11	34
Shunting	37	2	5
Survival of patients receiving radiotherapy			
Total	59		
Died	25		
Living			
0 to 3 years	10		
3 to 5 years	7		
5 to 10 years	10		
10 to 15 years	1		
15+ years	6		
Three-year survival rate			
Total	44		
Died	15		
Lived 3 years	29	(66%)	
Five-year survival rate			
Total	33		
Died	13		
Lived 5 years	20	(61%)	

*Patients who died within six days after operation

shunting because the patient had recovered well until the moment of his death on his seventh postoperative day.

The efficacy of radiotherapy in the treatment of these tumors is well demonstrated by the long-term survival of 7 out of 10 patients treated by external irradiation without attempted removal or shunting.

The ectopic pinealomas are not included in the final analysis because the surgical problem is not related to that with which this paper deals, but the effect of ionizing radiation on tissue of pineal origin is strikingly illustrated by the 3 long-term follow-ups on the 4 patients with surgically proved ectopic pineal tumors.

Table 5 presents the information which convinces us that radiotherapy, plus shunting when required, is the treatment of choice in these 2 conditions. By cutting the operative mortality from 34% to 5%, shunting spares many more patients to receive radiation therapy, which offers a three-year survival rate of 66% and a five year survival rate of 61%.

SUMMARY AND CONCLUSION

1. The operative mortality in direct surgical approach for excision or biopsy of third ventricle tumor, other than colloid cyst, or of pineal tumor is 34%.

2. The operative mortality from a shunting procedure to relieve obstructive hydrocephalus due to third ventricle tumor or pinealoma is 5%.

3. Radiation therapy in these 2 conditions in patients who have had partial removal of a tumor, biopsy, shunting procedure, or no surgery (if no hydrocephalus was present) provides a 61% five-year survival rate.

4. The preferred method of treatment, therefore, is that which spares the patient this great operative risk and gives him an opportunity to share in a high chance at a long-term, useful survival by radiation alone or by radiation plus shunting when obstructive hydrocephalus is present.

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Ophthalmologic aspects of diagnosis and localization of subdural hematoma

An analysis of 389 cases and review of the literature

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VARIOUS OCULAR SIGNS have been mentioned in case reports of intracranial hematomas during the past seventy-four years. Conflicting opinions have been presented concerning their value in diagnosis and accuracy in localization of the lesion. This study offers a review of the pertinent literature and an analysis of objective findings referable to the visual system in a recent large series of subdural hematomas.

REVIEW OF LITERATURE

The presence of a dilated, fixed pupil on the same side as an intracranial hematoma has been known since 1887, when Macewen[1] described such in fractures of the skull with large effusions of blood in the middle fossa. He suggested that the dilated pupil was due to increased intracranial pressure inhibiting function of that cerebral hemisphere and projected a table of the effects of this pressure:

Pressure	*Action of brain*	*Effect on pupil*
Very severe	Marked loss of function	Dilated, fixed
Slight to moderate	Decreased function	Contracted, sluggish
Removal of pressure	Restored function	Normal, reactive

This phenomenon of a subdural or epidural hematoma initially producing pupillary dilation, then constriction, and, finally, nonreactive dilation was affirmed by Schorcher,[2] who believed the increased intracranial pressure stimulated a homolateral cerebral sympathetic center. Neither of these theories would be compatible with modern neurophysiologic evidence that such supranuclear disturbance would produce bilateral signs.

In 1938, Jefferson[3] described the relationship of uncal herniation and direct involvement of the oculomotor nerve to produce a fixed and dilated pupil. Subsequently, many investigators have studied the various features of the "tentorial pressure cone." Reid and Cone[4] reported 10 cases of fixed, dilated pupil resulting from ipsilateral cerebral compression, noting direct pressure on the third nerve by the herniated portion of the hippocampal gyrus at 6 autopsies, 3 of which revealed occipital lobe infarction. They then made an experimental study of the mechanism by extradural compressive lesions in monkeys, obtaining progressive ipsilateral pupillary dilation and ptosis by tentorial herniation, but occipital lobe infarction was not elicited. The state of pupillary disturbance in 8 cases of chronic subdural hematoma (7 unilateral and 1 bilateral) was studied by Kaplan.[5] He found 5 of the 8 patients had misleading ipsilateral pyramidal tract signs. In contrast, 6 had a unilateral fixed, dilated pupil on the same side as the lesion and one with bilaterally dilated pupils had bilateral hematomas. He suggested that bilateral lesions may be present if there is no inequality of the pupils and subdural hematoma is found on one side. Kennedy and Wortis[6] stated that, in their series of 72 cases of acute subdural hematomas, 42 subjects had unequal pupils and that the dilated pupil was 3 times more accurate than hemiparesis in localizing

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the side of the lesion. Papilledema was present in 53% of the 48 cases of chronic subdural hematomas reported by Kunkel and Dandy,[7] yet other ocular signs were mentioned in only 2 cases; 1 patient had a large pupil on the side of the lesion, and the second had bilateral ptosis, sluggish pupils, and loss of upward gaze. Govan and Walsh[8] studied 54 adults in a general review of subdural hematoma in all age groups and stated that "careful observation of the pupils is of greatest possible importance as a unilateral dilatation usually signifies the side of the lesion." They based this conclusion on 6 cases, of which 5 included ipsilateral pupillary dilation.

Browder,[9] however, believed that clinical signs were unreliable in localizing the side of the hematoma. He found anisocoria in 46% of 289 patients but stated that a widely dilated pupil was present on the same side as the lesion in only 11% and on the opposite side in 29%, the remaining 6% apparently having bilateral hematomas. Similarly, hemiparesis was present in 166 of the 289 cases but was ipsilateral in 64 (22% of the entire series). Sherman and Krumholz[10] reported a fatal case of subdural hematoma with clinical signs of ipsilateral dilated, fixed pupil and ipsilateral hemiplegia. Autopsy revealed a large hippocampal herniation flattening the oculomotor nerve and producing a severe notching of the opposite cerebral peduncle. Clark and Gooddy[11] reported 2 cases of acute subdural hematoma that presented with ipsilateral oculomotor nerve palsy as the only definite neurologic abnormality. Bisgaard-Frantzen and Dalby[12] reviewed 12 cases of acute subdural hematoma and reported that 9 revealed fixed, dilated pupil ipsilateral to the lesion. Javalet, Davost, and Tuset[13] tried to use ocular manifestations to localize the side of the lesion in 19 patients who had ipsilateral pyramidal tract signs from a group of 432 with intracranial hematomas. In this selected group of 19, 5 presented ocular signs, 2 having a fixed, dilated pupil ipsilateral to the subdural collection.

The difficulties in proper examination of the visual fields have restricted adequate clinical investigation of the incidence of visual disturbance. Maltby[14] reported 7 cases of homonymous hemianopsia (4 definite, 3 probable) among 62 surgically verified subdural hematomas. The hemianopsia was contralateral in 5 and ipsilateral in 1, and the subdural hematoma was central interhemispheral in the seventh. Of the 7 patients, 2 died. Both autopsies revealed uncal herniation on the side contralateral to the hemianopsia, although occlusion of the posterior cerebral artery was not found and the appearance of the striate cortex was not described. However, Maltby believed that the field defects were due to a deficiency in circulation of the posterior cerebral artery subsequent to the herniation. The larger pupil was ipsilateral in 4 of the 6 patients with unilateral hematomas.

Retinal hemorrhages in association with papilledema, conjugate deviation of the eyes, paralysis of other cranial nerves (particularly the abducens), and nystagmus have been occasionally observed, but it has not been suggested that any of these signs has localizing significance. Govan and Walsh[8] believed that nystagmus and limitation of upward gaze in subdural hematoma reflected only a nonspecific disturbance in conjugate movement of the eyes. However, Johnson and Yates[15] described 4 patients with expanding supratentorial lesions (1 with bilateral subdural hematoma) who had a loss of upward gaze, and subsequent autopsy in 2 of these demonstrated posterior tentorial herniation with distortion of the midbrain. They proposed that disturbance of upward gaze is a valuable sign of dorsal midbrain compression.

ANALYSIS OF CURRENT MATERIAL

A review of the general features of clinical presentation, surgical management, and prognosis in 389 cases of proven subdural hematoma was recently made by McKissock, Richardson, and Bloom.[16] The medical records of this same group of patients are analyzed in this report for objective signs referable to the visual system (Table 1). Cases associated with or complicated by other forms of intracranial hemorrhage were omitted. The same system of classification is presented here as was used in the primary review,[16] based on the rate of evolution of symptoms after trauma. Thus, "acute" cases presented urgent symptoms within three days after trauma, "subacute" presented within four to twenty days, and "chronic" presented after twenty days. Cases

TABLE 1
INCIDENCE OF OPHTHALMOLOGIC SIGNS IN SUBDURAL HEMATOMA

	Acute	*Subacute*	*Chronic*	*Total*
Pupillary inequality	47 (57%)	25 (28%)	44 (11%)	116 (30%)
Papilledema	1 (1%)	14 (15%)	48 (22%)	63 (17%)
Third nerve palsy	3 (4%)	7 (8%)	8 (4%)	18 (5%)
Sixth Nerve palsy	0	4 (4%)	10 (5%)	14 (4%)
Homonymous hemianopsia	0	4 (4%)	7 (3%)	11 (3%)
Limited upward gaze	1 (1%)	3 (3%)	2 (1%)	6 (2%)
Nystagmus	1 (1%)	0	5 (2%)	6 (2%)
Total	82	91	216	389

with no history of trauma were classified on the basis of total duration of symptoms.

Pupillary inequality was the most common ophthalmologic sign in this series. Its frequency varied inversely to chronicity; thus, it was noted in 57% of the acute cases, 28% of the subacute, and 11% of the chronic. Of a total of 116 patients with anisocoria, 101 were found to have unilateral hematoma. Among these, the larger pupil occurred on the same side as the lesion in 92 (91%) and contralateral to the lesion in 9 (9%). In the remaining 15 cases of bilateral lesions, the larger pupil was usually on the same side as the larger hematoma. Other signs of third cranial nerve dysfunction were present in 18 cases, ptosis being the second most common sign in the series. Complete third nerve paralysis was observed in only 3 cases.

Papilledema was exceedingly rare (1%) in the acute cases, increasing in incidence to 22% among the chronic cases. When optic disk con-

TABLE 2
HOMONYMOUS HEMIANOPSIA IN SUBDURAL HEMATOMA

			Laterality of neurologic signs					
Classification	*Sex*	*Age*	*Hematoma*	*Hemianopsia*	*Hemiparesis*	*Sensory loss*	*Increased reflexes and Babinski sign*	*Comments*
Subacute	F	84	Left	Right	Right	No	Right	Aphasia; satisfactory recovery
Subacute	M	51	Right	Left	No	Left	Right (ipsilateral)	Hemianopsia noted on third day after clot evacuation and absent by fifth day
Subacute	F	73	Left	Right	Right	Right	Right	Aphasia, skull fracture; signs were permanent
Subacute	F	59	Left	Right	Right	No	Right	Initial improvement after clot evacuation, then reaccumulation caused death; hemorrhagic infarction of left occipital lobe
Chronic	F	63	Left	Right	Right	Right	Right	Complete recovery
Chronic	F	69	Left	Right	No	No	Right	Complete recovery
Chronic	M	75	Right	Left	Left	No	Left	Complete recovery
Chronic	M	57	Right	Left	Right (ipsilateral)	No	No	Right ophthalmoplegia; satisfactory recovery
Chronic	F	52	Left	Right	Right	Right	Right	Mild dysphasia; complete recovery
Chronic	F	78	Left	Right	Right	Right	Right	Aphasia; steady improvement
Chronic	M	74	Left	Left (ipsilateral)	Left (ipsilateral)	Left (ipsilateral)	Left (ipsilateral)	Hemianopsia was initial sign; progressive deterioration for 2 months before admission; death 3 days after evacuation of clot; massive infarctions in both hemispheres

TABLE 3
ACCURACY OF UNILATERAL OCULAR SIGNS IN LOCALIZING SIDE OF HEMATOMA

	Number of unilateral hematomas with signs	*Relation of sign to hematoma*	
		Ipsilateral	*Contralateral*
Pupillary dilatation	101	92 (91%)	9
Abducens nerve palsy	11	11 (100%)	0
Nystagmus on lateral gaze	4	3 (75%)	1
Homonymous hemianopsia	11	1	10 (91%)

gestion was asymmetric in appearance or was in conjunction with retinal hemorrhages, there was no correlation to site of the lesion.

The 14 instances of sixth cranial nerve disturbance were found only in subacute and chronic cases. Loss of lateral gaze was unilateral in 11 patients and was ipsilateral to the lesion in all of them. Of the remaining 3 subjects with bilateral abducens palsy, 2 had bilateral subdural hematomas.

In 10 of the 11 relatively alert patients with demonstrable homonymous hemianopsia, the field defect was contralateral to the side of the subdural hematoma. In 9 patients, hemiparesis was present on the same side as hemianopsia, and 4 of these had disturbances of sensation on the same side. In these patients, the motor, sensory, and visual field defects tended to coincide in both appearance and subsequent recovery. There were 2 deaths subsequent to evacuation of the hematoma, 1 due to reaccumulation of subdural blood, and both autopsies revealed hemorrhagic infarction in the occipital lobe. However, 1 of these subjects had hemianopsia and motor and sensory signs ipsilateral to a massive hematoma, and autopsy showed widespread infarctions in both cerebral hemispheres. Detailed analysis of this group of cases is presented in Table 2.

Nystagmus of lateral gaze was noted in 6 cases: ipsilateral to the lesion in 3, contralateral in 1, bilateral in 1 case of bilateral hematomas, and unspecified in 1 unilateral case. Limitation of upward conjugate gaze was found in 6 patients, 5 of whom also had disturbance of the third or sixth cranial nerves ipsilateral to the hematoma. Autopsy in 1 case revealed midbrain and pontine hemorrhages.

The accuracy of various unilateral ocular signs in localizing the side of the hematoma is presented in Table 3.

DISCUSSION

The general features such as headache, a rapidly fluctuating state of consciousness, and other physical signs suggesting the diagnosis of subdural hematoma are not within the scope of this discussion. However, the mechanisms by which the supratentorial space-occupying lesion may produce various and misleading neurologic signs are worthy of perusal. In addition to distortion of the cerebral hemisphere and disturbance of its normal function by either mechanical compression or interference with its blood supply, an expanding subdural hematoma may cause herniation of the mesial portion of the temporal lobe through the tentorial opening; this compresses the adjacent structures and produces signs which are not limited to subdural hematoma but which may result from any supratentorial lesion that is sufficiently lateralized and large enough to produce the herniation. Pupillary dilation and ptosis appear to be the earliest signs of such displacement.[4] Sunderland,[17] in a detailed investigation of the nature of herniation of the brain through the tentorial aperture, stated that supratentorial expanding lesions produce effects about the tentorial notch which follow a characteristic pattern that can be expressed in terms of displacement and deformation of the structures that are arranged about the opening. The appearance of clinical signs associated with this complication depends not only on the precise anatomic relationships, and thus the extent to which structures are deformed, but also on the rate at which this occurs. He considers that the pupilloconstrictor fibers are concentrated over the superior arc of the oculomotor nerve from the midbrain to the cavernous sinus; hence, they are most vulnerable to compression from above. In herniation of the hippocampus over the tentorial edge, the superior portion of the ipsilateral third nerve is first to be affected and early changes in the pupil would be expected. Irritation of subjacent fibers would lead to constriction of the pupil, but this phase is usually

short. Further deformation, involving somatic fibers of the nerve, results in gradual failure of conduction and complete third nerve paralysis. Before this stage, the opposite eye may also show pupillary abnormalities progressing to bilaterally fixed and dilated pupils.

The high incidence of misleading pyramidal tract signs in supratentorial mass lesions has prompted several detailed investigations. Although not the first to describe the clinical syndrome, Kernohan and Woltman[18] proved by autopsy studies that homolateral tract signs in brain tumors were produced by tentorial notching of the cerebral peduncle on the contralateral side; this mechanism has been confirmed by a number of other reports.[3,4,9,10,17] The dynamic nature of this process of tentorial herniation causes clinical signs which may fluctuate rapidly. Careful and repeated examinations are necessary to observe these changes and evaluate their significance.

The visual field defects in the present series cannot be explained on a single pathophysiologic basis. Possible mechanisms are [1] compression of the posterior cerebral artery, [2] compression of the anterior choroidal artery affecting the optic tract, lateral geniculate body, or anterior optic radiations, and [3] compression of the optic tract, optic radiations, or visual cortex. Of our 11 cases of homonymous hemianopsia, 10 were contralateral to the side of the subdural and were generally associated with similarly contralateral pyramidal tract signs, sensory disturbance, and dysphasia when involving the dominate side, indicating a diffuse dysfunction of the cerebral hemisphere. However, in the complete series of 389 patients with hematomas, 159 had pyramidal tract signs and 39 had dysphasia;[15] therefore, other factors such as the patient's state of alertness and the chronicity of the lesion must be involved to permit recognition of only 11 cases of hemianopsia. Sunderland[16] and Maltby[14] emphasized the role of compression of the posterior cerebral artery or its calcarine branches by tentorial herniation to produce visual field defects. Although this pathogenesis was compatible with the postmortem studies in 1 of the 2 deaths in our group of 11 patients with hemianopsia, the close correlation of the clinical signs of diffuse hemispheral dysfunction in this group indicates that direct cerebral compression may be responsible for the visual field defect in many of these cases.

SUMMARY

The incidence and localizing value of ocular signs in a series of 389 cases of proven subdural hematoma are presented, and the pertinent literature is reviewed. When present, the various unilateral ocular signs of pupillary dilation, abducens nerve palsy, and homonymous hemianopsia assisted in lateralizing the hematoma in over 90% of the patients. The mechanism of tentorial herniation producing these signs as well as causing misleading ipsilateral pyramidal tract signs is discussed. The necessity of careful and repeated examinations for the presence of such signs is emphasized.

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Seventh International Congress of Neurology

The Seventh International Congress of Neurology will be held in Rome, Italy, September 10-15, 1961. The scientific sessions will be conducted in the Auditorium de Via Della Conciliazione (Palais Pius).

The following pertinent information can be offered by the United States Joint Committee on International Neurological Affairs at this time.

The Congress will have 3 **categories of membership:** *active*, open to members of the constituent national neurological societies of the Congress; *associate*, open to qualified physicians and scientists having an interest in the Congress; and *adjunct*, open to interested nonprofessionals and to families of members of the Congress. **Registration fees** are $15 (or equivalent in Italian lire) for active members; $10 for associate members; $5 for adjunct members. **Banquet and dance** will be held in the Palais Des Traditions Populaires, Tuesday evening, September 12, 1961. Tickets are $8 for the banquet and $3 for the dance and must be purchased at the time of registration. Registration fees are not refundable.

United States **registration forms** are in process of preparation. They may be applied for and returned with designated fee to the member of the United States national committee designated below. He will also handle the submission of papers to the Secretary General of the Congress in Rome.

The **scientific program** will consist of reviews of 3 major topics and free papers. The major topics will be [1] toxic and metabolic disorders of the nervous system, under the direction of Dr. H. Houston Merritt of New York; [2] neurologic changes associated with cardiovascular and respiratory diseases, under the direction of Dr. G. Bodechtel of Munich; and [3] aphasia and disorders of language, under the direction of Dr. Macdonald Critchley of London. Communications accepted for the program will be presented according to the digest system adopted at the Brussels International Congress in 1957. Accordingly, the papers will be grouped by subject matter and assigned to a digest director who will synthesize and present the substance of all the papers assigned to his group. Authors of communications will not present the text of their papers except in special instances. All communications, whether related to a major topic or not, will be published or summarized in precirculated booklets, provided they reach the Office of the Secretary General of the Congress on or before April 15, 1961.

Titles and 1,000-word texts of all communications should be submitted *in triplicate* to the designated member of the United States national committee before March 15, 1961, to be forwarded by him to the Secretary General of the Congress in Rome. We are informed that those related to the major topics will be given priority over free communications. If texts are not written in English or French, they should be accompanied by 500 word summaries in these languages.

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Neurology

BOOK REVIEWS

Progress in Neurology and Psychiatry: An Annual Review

edited by E. A. Spiegel, M.D., Vol. 14, 656 pp., Grune & Stratton, New York, 1959. $12

As has been the case for the last thirteen years, this the fourteenth volume of Dr. Spiegel's annual review of neurology and psychiatry will help one to keep up to date in the advances that have been made in these fields. Recent progress in the basic sciences has been perhaps more conspicuous than that in the clinical disciplines of neurology and psychiatry, but both are extensively dealt with, the total number of references exceeding 4,000.

The various reviewers are authorities in their own fields. The sections are well written and bring together much of the current research in neurology, neurosurgery, and psychiatry. These volumes will continue to be important reference sources.

R.N.D.

Exploration du Cerveau Human par Electrodes Profondes

by Michel Ribstein, 129 pp., Masson & Cie, Paris, 1960. $5.50

This monograph is supplement Number 16 of *Electroencephalography and Clinical Neurophysiology*.

The work is divided into 2 main parts, the first devoted to the clinical presentation and description of technical details for depth electrography on 6 cases studied by the author during the year of 1955 to 1956, which he spent at the Division of Neurological Surgery at the Johns Hopkins Hospital in Baltimore. The second part constitutes an extensive review of the literature, with critical comments included in the discussion of each chapter.

Although the small number of cases which comprise the author's personal experience may seem a poor justification for a monograph on depth electrography in man, some important factors are brought up in the study. Probably the most important concept discussed here is that of criteria for selection of patients in whom depth electrodes should be implanted. In all the cases, the main objective of this type of study was the attempt to detect deep foci of abnormality with the hope that their extirpation might improve the patient's condition. This was the only possible help for these patients because anticonvulsant medication had been ineffective in all of them.

This is, we think, the only justifiable reason for the use of a method that is potentially dangerous for the patient. Volunteers, whether of sane or diseased mind, cannot understand all the details of the procedure and therefore cannot comprehend the possibilities of damage to the brain involved in a technic that requires the insertion of multiple metallic wires or needles into the cerebral substance. Only the possibility of therapeutic benefit can justify this technic in man.

The author points out the negligible number of immediate complications but discusses openly experimental studies that have shown the presence of definite though not clinically de-

tectable alterations produced by chronic implantation of electrodes.

Another important observation constitutes the abnormal discharges recorded up to several hours and even days after implantation of electrodes. These disappear eventually and are probably the equivalent of injury potentials found in animals. This should make our interpretation of results of acute depth recordings more guarded and qualified.

Lack of correlation between clinical and electrical signs is, according to the author, a frequent occurrence. Thus, when electrical after-discharges were produced by stimulation of deep structures, they were not always accompanied by clinical manifestations. In some cases, when clinical manifestations were produced by stimulation, consecutive seizures varied in type and intensity regardless of constancy of parameters of stimulation. This brings up the point, considered in later discussion by the author, of the influence of background electrical activity and also, to a lesser extent, of the patient's personality on the type of seizure that may occur from stimulation of any given structure.

All these points are carried along in a more general way in the second part of the monograph. This part is devoted to description and discussion of the literature on depth electrography. It is divided by subtitles covering indications and recording in neurologically normal subjects during waking and sleep conditions, as well as during stimulation. Electrical activity in convulsive disorders follows. Finally, depth recording in mental patients and in nonepileptic neurologic conditions is discussed.

The bibliography includes 280 references.

Although no new technical contributions and only few original experimental data are offered, this monograph has a definite place in the neurologic literature due to the straightforward discussion of some points which in the past had remained obscured by unilateral points of view expressed in individual papers. The author brings out and clarifies many of these points in a stimulating way which undoubtedly will promote further and more ample discussion. The extensive bibliography also makes this publication worthy of any good neurologic library.

F.M. and F.T.

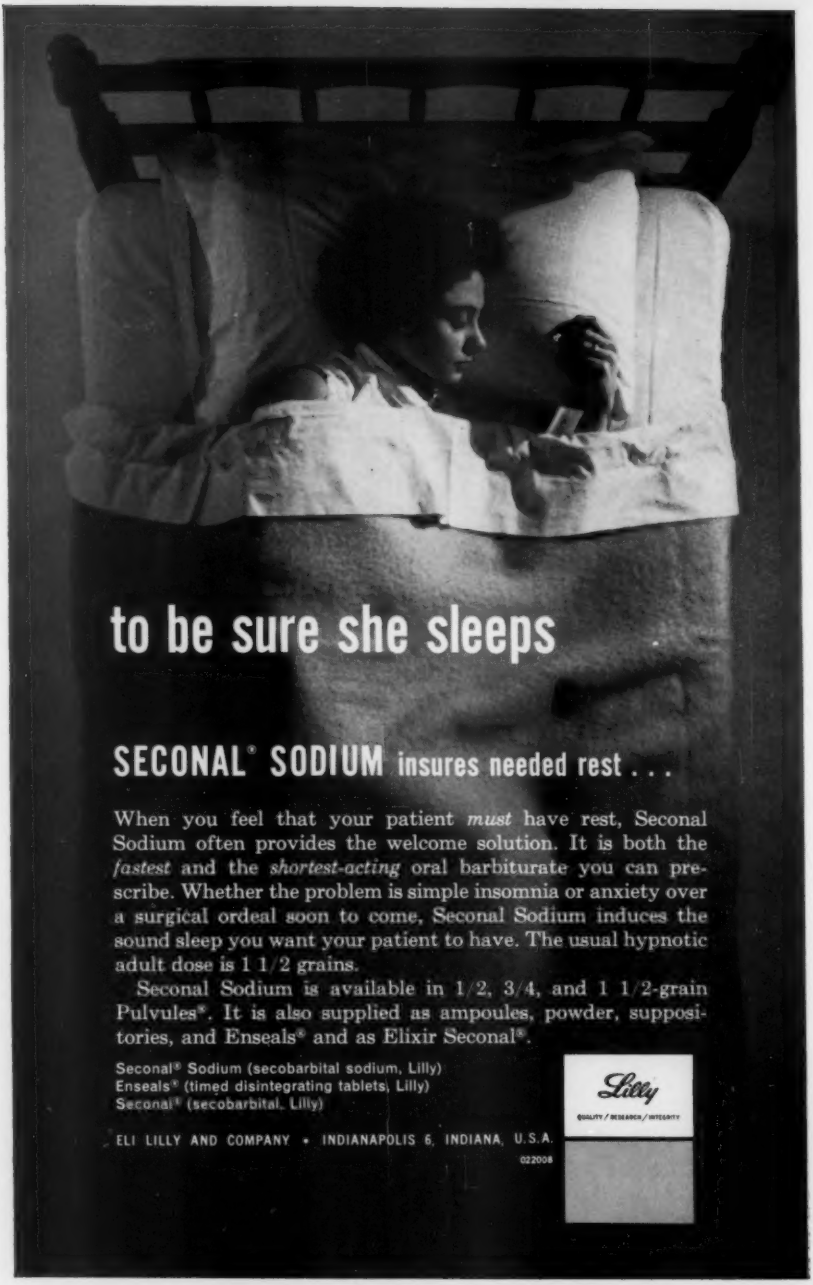
Thymectomy for Myasthenia Gravis

edited by Henry R. Viets, M.D., and Robert S. Schwab, M.D., 143 pp., ill., Charles C Thomas, Springfield, Ill., 1960. $7.

This monograph will be of value to the physician who treats patients with myasthenia gravis. The authors are authorities in their fields and write after extensive experience with thymectomy at the Massachusetts General Hospital. Each section of the book is concise and well-written. Considering that there are 6 contributors, there is very little repetition and the writing styles blend nicely. The book begins with an interesting historical review of thymectomy for myasthenia gravis by Dr. Viets. There follows a brief review of the general clinical features and medical treatment of the disease by Dr. Schwab, who then presents his program for the medical management of the myasthenic patient before, during, and after thymectomy. This section in particular should be read by all physicians who may have occasion to manage the myasthenic patient during thymectomy, for the author's experience is extensive and, with his technics, the mortality has been reduced to 3%. Dr. Castleman discusses the pathology of thymic lesions in myasthenia gravis and presents excellent illustrations. Dr. Lawrence Robbins reviews the x-ray diagnosis and treatment of thymic lesions and reproduces typical roentgenograms. Dr. Richard H. Sweet presents the surgical technics of thymectomy, and Dr. J. L. Vanderveen discusses the anesthetic management. The final chapter, written jointly by Drs. Schwab and Viets, is an evaluation of results from thymectomy in the series of patients from the Myasthenia Gravis Clinic of the Massachusetts General Hospital. They further correlate their series of patients with those of other investigators and conclude that, "when properly carried out in selected patients, thymectomy offers the patient the best chance for complete and possibly permanent remission from myasthenia gravis."

While this study (as the authors admit) will not resolve fully the controversy that exists regarding the value of thymectomy in patients with myasthenia gravis, it is recommended to neurologists as a lucid summary of our knowledge of the subject to date.

K.R.M.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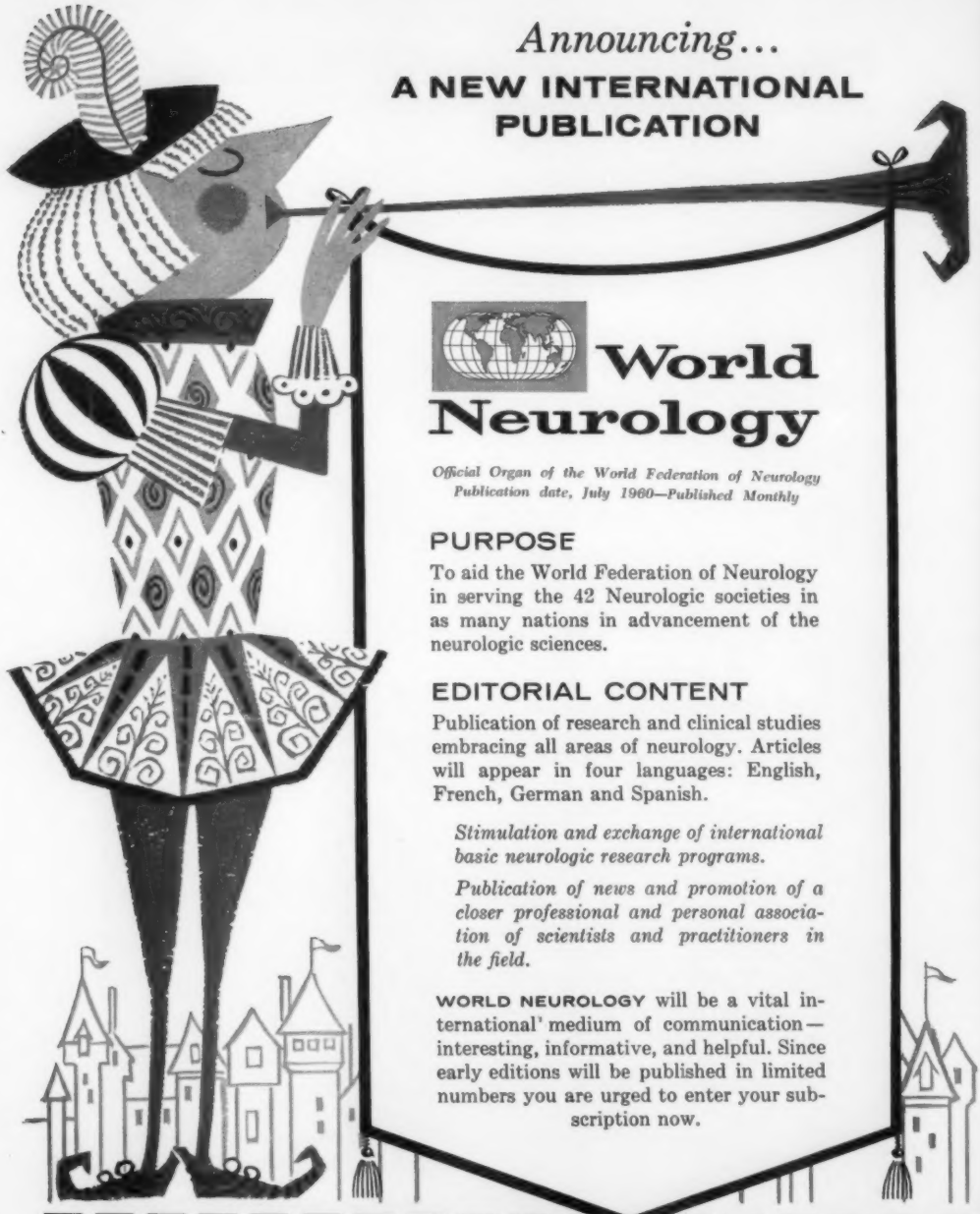

World Neurology

Official Organ of the World Federation of Neurology
Publication date, July 1960—Published Monthly

PURPOSE

To aid the World Federation of Neurology in serving the 42 Neurologic societies in as many nations in advancement of the neurologic sciences.

EDITORIAL CONTENT

Publication of research and clinical studies embracing all areas of neurology. Articles will appear in four languages: English, French, German and Spanish.

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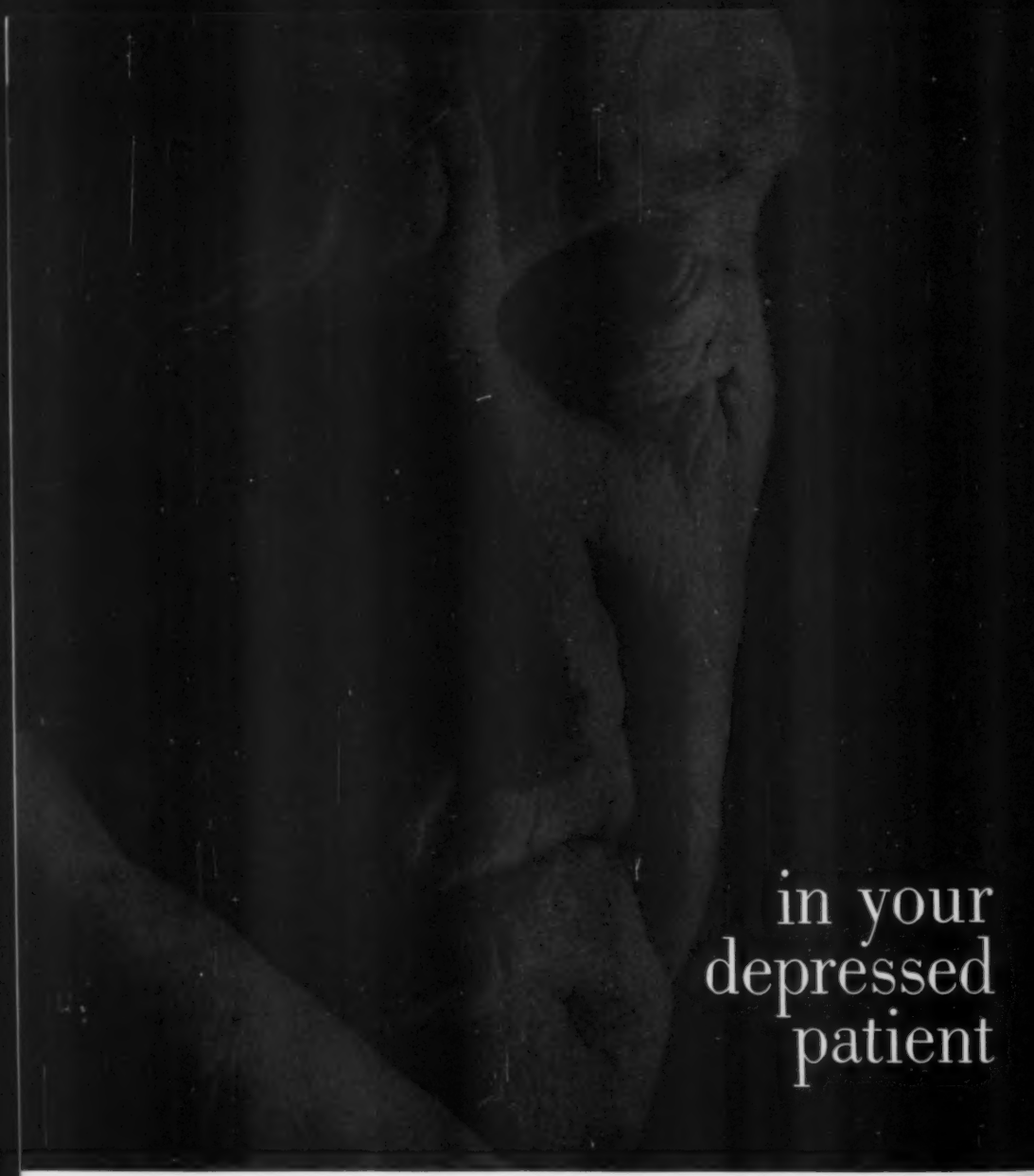

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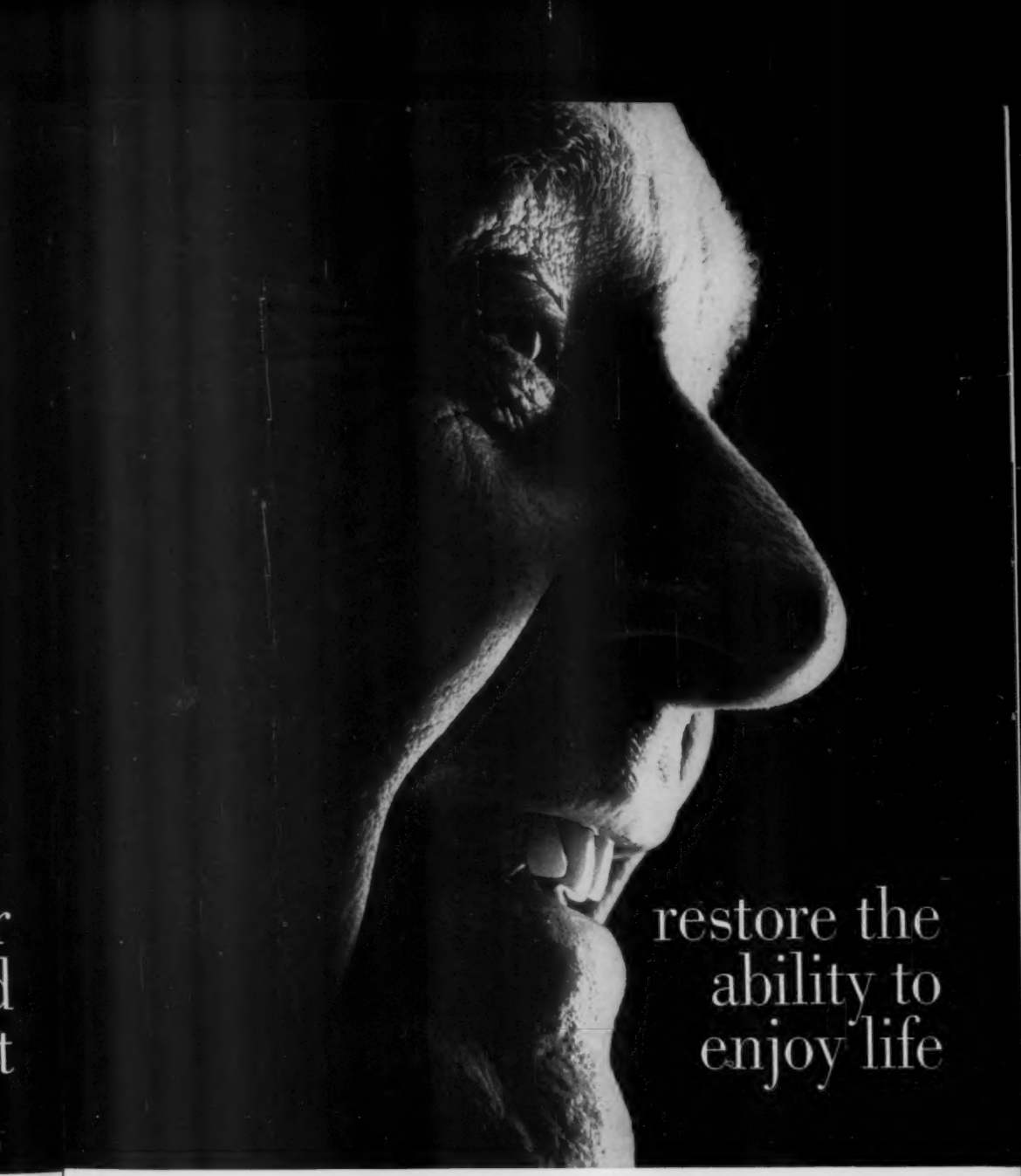

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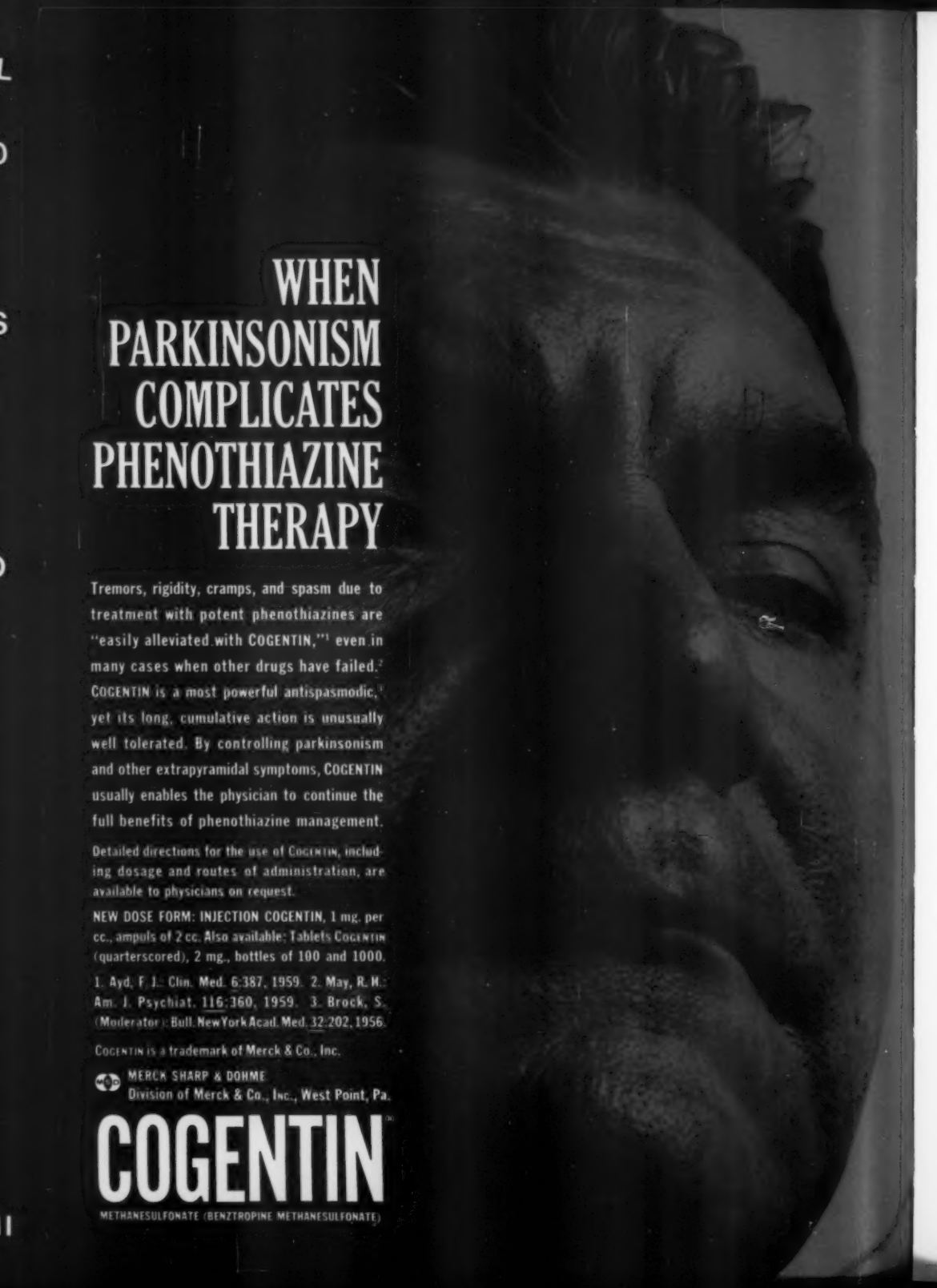

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NINDB Sponsors Mission to Russia The National Institute of Neurological Diseases and Blindness is sponsoring a second mission of American scientists to the U.S.S.R., this time to review the conditions of maternal and child care in Russia. The mission is scheduled for mid-October 1960. Included in the NINDB group are Stewart H. Clifford, Chairman of Boston Lying-In Hospital; Allan C. Barnes, Professor and Chairman of the Department of Obstetrics and Gynecology at Western Reserve University; Katherine Bain, Deputy Chief of the Children's Bureau of the Department of Health, Education, and Welfare; Bernard D. Greenberg, School of Public Health, University of North Carolina; Edith L. Potter, Chicago Lying-In Hospital; and Fred S. Rosen, Children's Hospital, Boston. The group is especially interested in studying in the U.S.S.R. methods of indoctrination and preparation for pregnancy; perinatal pathology; newborn and nursery care; child care programs for youngsters up to 6 years of age; and immunization programs. Other items to be investigated are methods for detection of neurologically disabled children; care of the handicapped; management of prematurity, kernicterus, and infections of the newborn; and methods of collection and analysis of health data and statistics... The first NINDB-sponsored mission to the Soviet Union, under the direction of Francis M. Forster, took place in the winter of 1958 and was designed to review the status of neurophysiology and neuropharmacology in the principal brain institutes and neurologic research hospitals.

WFN Admits U.S.S.R. to Membership The officers and official delegates of the World Federation of Neurology have admitted to membership the Soviet Association of Neuropathologists and Psychiatrists (Moscow) as the constituent national society of the WFN, representing the Union of the Soviet Socialist Republics. This action came in response to an application for WFN membership by Professor Dr. S. A. Sarkisov, President of the Soviet Union's Association of Neuropathologists and Psychiatrists and member of the Soviet Academy of Medical Sciences... Other nations recently added to WFN membership through their national neurologic societies are Lebanon, Finland, and the East German Republic... The WFN now has representation from 48 nations and a total individual membership of approximately 10,000 neurologists.

Epilepsy Institute Holds Annual Meeting Legal, scientific, and historical aspects of epilepsy were discussed by prominent authorities during the Twelfth Western Institute on Epilepsy, held in Kansas City in September. WORLD NEUROLOGY Editor, Charles M. Poser, Associate Professor of Medicine in the Section of Neurology at the University of Kansas, presided at two of the sessions and served as a moderator for a panel on convulsions.

van Bogaert Visits the United States Ludo van Bogaert, Director of the Institut Bunge in Antwerp and President of the World Federation of Neurology, has completed his first tour of the United States. He was accompanied by Madame van Bogaert. His tour included visits to the Neurological Institute of New York (H. Houston Merritt), New York Hospital (H. G. Wolff), New York University-Bellevue Hospital Neurologic Service (William K. Jordan), and the Neurologic Service of the Montefiore Hospital (Tiffany Lawyer and Harry Zimmerman). He also visited Richard L. Masland at NINDB in Bethesda where he lectured on "Acute and Subacute Encephalitides of Current Interest." His trip culminated in an excursion to Puerto Rico with William F. Windle to visit the NINDB Laboratory of Perinatal Physiology in San Juan and the NINDB colony of free-ranging monkeys inhabiting an offshore island.

NINDB Appropriation Increased The appropriation for the fiscal year 1961 of the National Institute of Neurological Diseases and Blindness is $56.6 million, the amount agreed upon by the Senate and House Conference Committee. This figure is approximately $5 million less than the Senate's recommendation, $12 million less than the House recommendation, and $17 million more than the executive budget estimate... The total 1961 NIH appropriation is $560 million, with an additional $30 million allocated for construction.

Windle Made Assistant Director of NINDB William F. Windle, Editor-in-Chief of EXPERIMENTAL NEUROLOGY and for the past six years Chief of Laboratory of Neuroanatomical Sciences, NINDB, has been appointed Assistant Director of that Institute. In his new post, Windle will serve as assistant and adviser to the NINDB Director, Richard L. Masland. His major concern, however, will be the development of the Laboratory of Perinatal Physiology, which is operated in collaboration with the School of Medicine of the University of Puerto Rico... Sanford L. Palay has replaced Dr. Windle as Chief of the NINDB Laboratory of Neuroanatomical Sciences.

International Symposium Evaluates Radiation Effects New findings on the response of the nervous system to ionizing radiations were presented by 42 authorities from 7 countries (including the U.S.S.R.) at a symposium September 7 through 9 at

Northwestern University. The sessions, which were chaired by Ray Snider, were jointly supported by the Atomic Energy Commission and the National Institute of Neurological Diseases and Blindness. The findings that were featured were studies by Roberts Rugh, indicating a very low radiation level is needed to produce a congenital abnormality in embryo rats; a study by Orville T. Bailey, suggesting that the effects of radiation on the nervous system are primary rather than secondary to vascular changes, confirming previous studies by Milton Brightman; and a presentation by Marcel Monnier (Basil, Switzerland), revealing that low doses of radiation alter electrical discharge patterns in the brains of mice. About 340 scientists attended the sessions.

New Members Appointed to NINDB Council and Board of Counselors

New members appointed by U. S. Public Health Service Surgeon General Leroy E. Burney to the National Advisory Neurological Diseases and Blindness Council for four-year terms are John E. Bordley, Professor and Director of the Department of Laryngology and Otology of the Johns Hopkins School of Medicine and Professor of Audiology and Speech at the University School of Hygiene and Public Health; H. Houston Merritt, Vice President in Charge of Medical Affairs and Dean of the Faculty of Medicine at Columbia University's College of Physicians and Surgeons and Director of the Neurology Service of the New York Neurological Institute; and Leonard Mayo, Executive Director of the Association for the Aid of Crippled Children, New York City. Drs. Merritt and Bordley fill the expired terms of John R. Lindsey and W. L. Benedict. Mr. Mayo succeeds the late H. L. Prentiss. The 12-member NANDB Council serves as an advisory board to the Surgeon General and to NINDB for the awarding of research and training grants (in the field of neurologic and sensory disorders) to medical schools and institutions... Recently appointed by NIH Director James Shannon to the NINDB Board of Scientific Counselors were Martin G. Larabee, Associate Professor of Biophysics at Johns Hopkins University, who succeeds Howard J. Curtis; and Eben Alexander, Jr., Professor of Neurosurgery at Bowman Gray School of Medicine, who succeeds A. Earl Walker. The 6-member Board of Scientific Counselors, composed of non-federal scientists, reviews, discusses, and makes recommendations relative to the research activities being conducted within NINDB's laboratories and clinics.

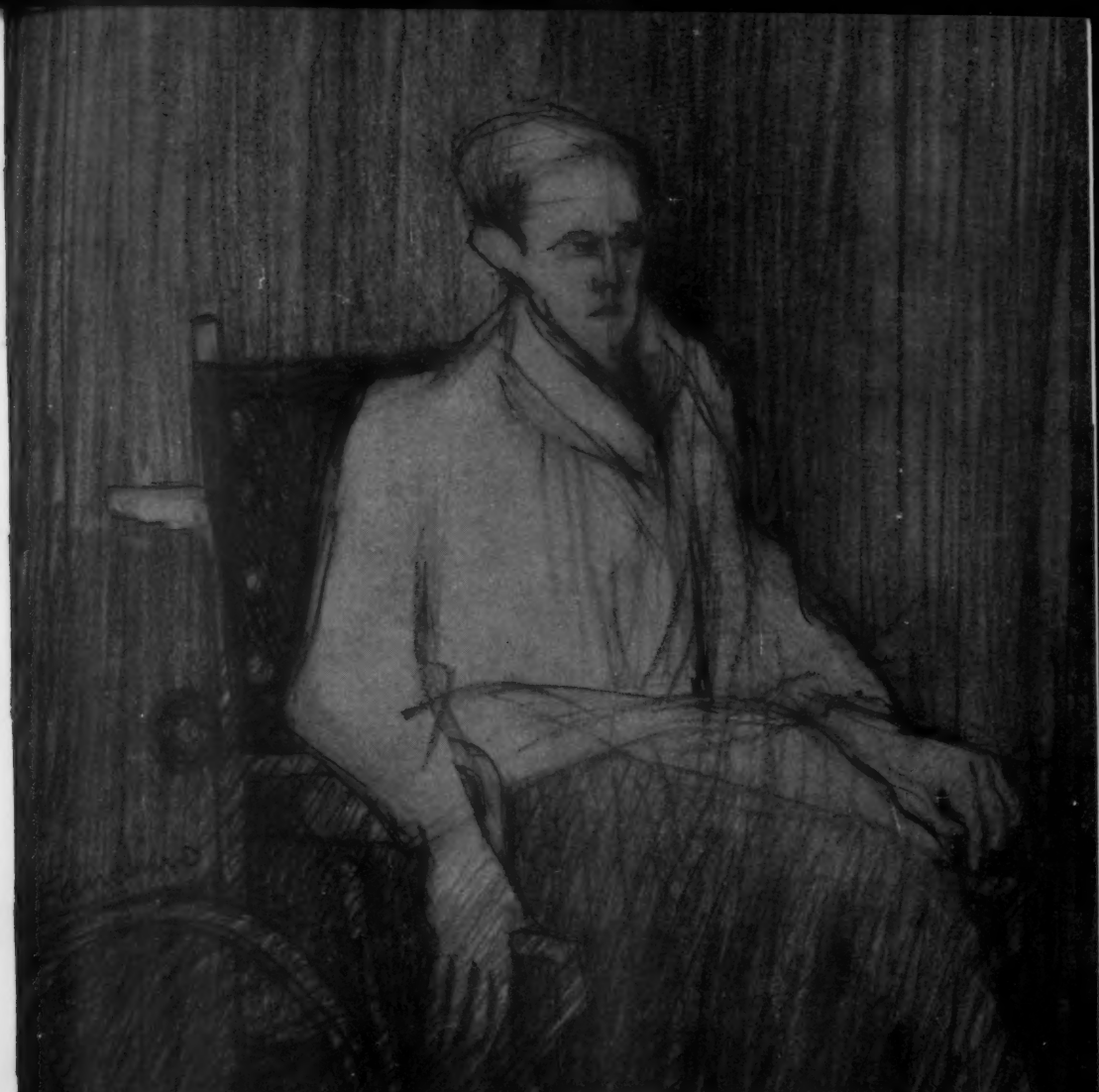
O'Leary to Manage U. S. Affairs at Rome Congress

James L. O'Leary, the national U. S. delegate, will manage registrations and the submission of titles and abstracts for the Seventh International Neurological Congress, to be held in Rome September 10 through 16, 1961. Bernard J. Alpers is the alternate delegate, and both represent the American Joint Committee (ANA and AAN) on International Neurological Affairs, of which

Roland P. Mackay is Chairman. Information regarding procedures of enrollment and submission of papers will appear as Announcements in NEUROLOGY. All inquiries relative to U. S. participation in the Congress should be forwarded to Dr. James L. O'Leary, Washington University School of Medicine, 660 South Kingshighway, St. Louis 10... Henry A. Riley is an honorary president and H. Houston Merritt a vice-president of the Congress.

Briefs At the Eighth World Congress of the International Society for the Welfare of Cripples, a 37-year-old confederation of national voluntary agencies, the Society changed its name to the International Society for the Rehabilitation of the Disabled; the new name indicates "a shift in thinking from the old benevolent paternalism of 'cripples' to the more positive concept of rehabilitation."... Wilder Penfield, founder and first Director of the Montreal Neurological Institute, was selected the NIH Lecturer on October 4. The subject of his address was "Conscious Experience -- What the Brain Records and Where."... Diagnostic and therapeutic problems of aphasia in children was discussed at an Institute on Aphasia, sponsored in September by the California Society for Crippled Children and Adults at Stanford University Medical School... Mrs. Abraham E. Pinanski, a member of the NINDB Advisory Council, was elected Honorary Member of the American Hospital Association in recognition of her contributions to the health field... Jack Masur, Associate Director for the National Institutes of Health and Director of the NIH Clinical Center, is the new President-Elect of the American Hospital Association... The Second International Medical Conference on Mental Retardation is scheduled for August 14 through 19, 1961, in Vienna, Austria.

Pearce Bailey



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References: 1. J. D. Young, Jr., W. S. Kiser and O. C. Beyer, **Antibiotic Med. & Clin. Therapy, 6**:(Suppl. 1), 53, 1959. 2. W. A. Leff, **ibid.**, p. 44. 3. R. E. Bagdon, L. O. Randall and W. A. Leff, **Ann. New York Acad. Sc., 82**:(Art. 1), 3, 1959. 4. J. C. Elia, **ibid.**, p. 52.

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**Abraham, W., in Green, J. R., & Steelman, H. F.: Epileptic Seizures, Baltimore, Williams & Wilkins Company, 1956, p. 132.*

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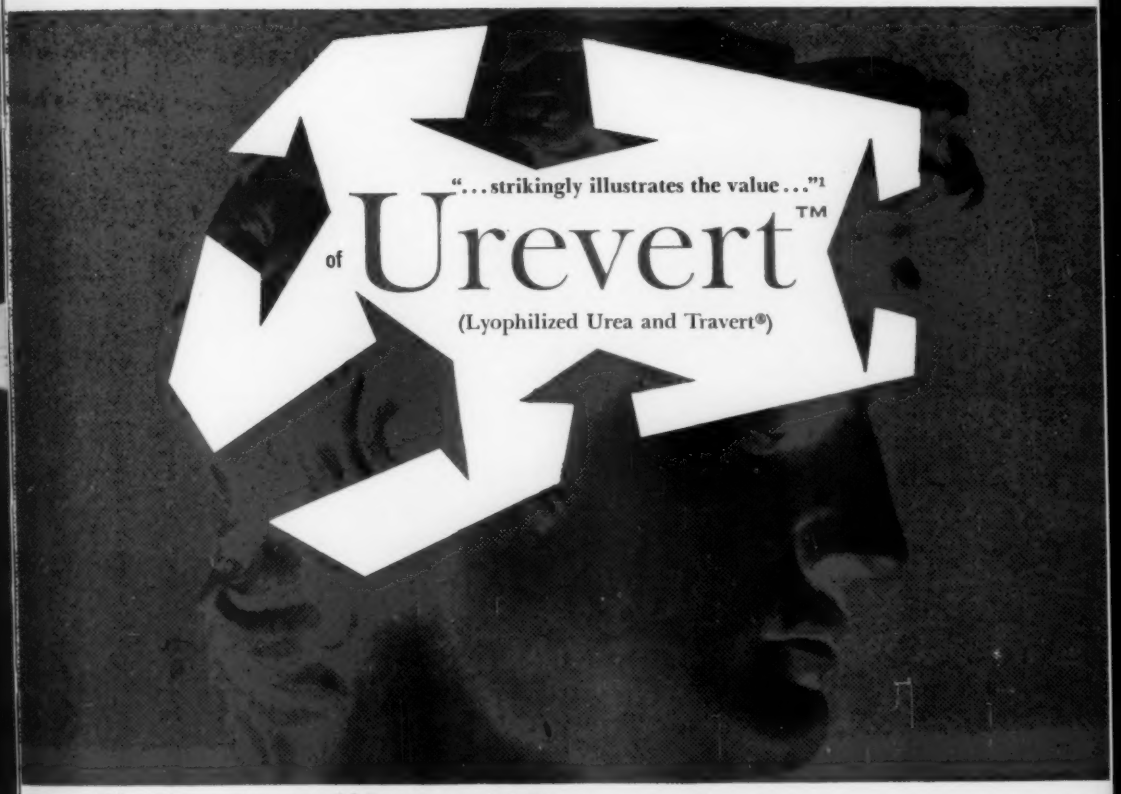

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1. Taheri, Z. E.: Urevert in Cranial Trauma and Brain Surgery, J. Internatl. College of Surgeons 32:389 (Oct.) 1959.
2. Javid, M.: Urea—New Use of an Old Agent, Reduction of Intracranial and Intraocular Pressure, The Surgical Clinics of North America, Philadelphia, W. B. Saunders Company, Aug. 1958, p. 907.

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Visual Field Defects after Penetrating Missile Wounds of the Human Brain

By Hans-Lukas Teuber, William S. Battersby, and Morris B. Bender

This study, contrary to previous reports, revealed a lack of congruence of visual field defects plotted for right and left eyes and suggested a need for revision of current anatomical notions about the optic radiation. From the research program of the Psychophysiological Laboratory, New York University-Bellevue Medical Center. 58 pages of illustrations. $4.75

Somatosensory Changes after Penetrating Brain Wounds in Man

By Josephine Semmes, Sidney Weinstein, Lila Ghent, and Hans-Lukas Teuber

Based on data from groups of subjects, this study questions the assumption that sensory representation for the left hand is a mirror image of that for the right, and indicates that the dissimilarity between the cerebral hemispheres involves such a basic aspect of behavior as tactile sensibility. The studies are part of a research program at the Psychophysiological Laboratory, New York University-Bellevue Medical Center. 9 graphs. $4.00

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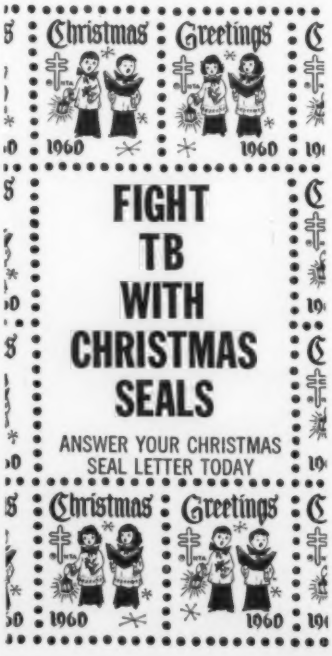

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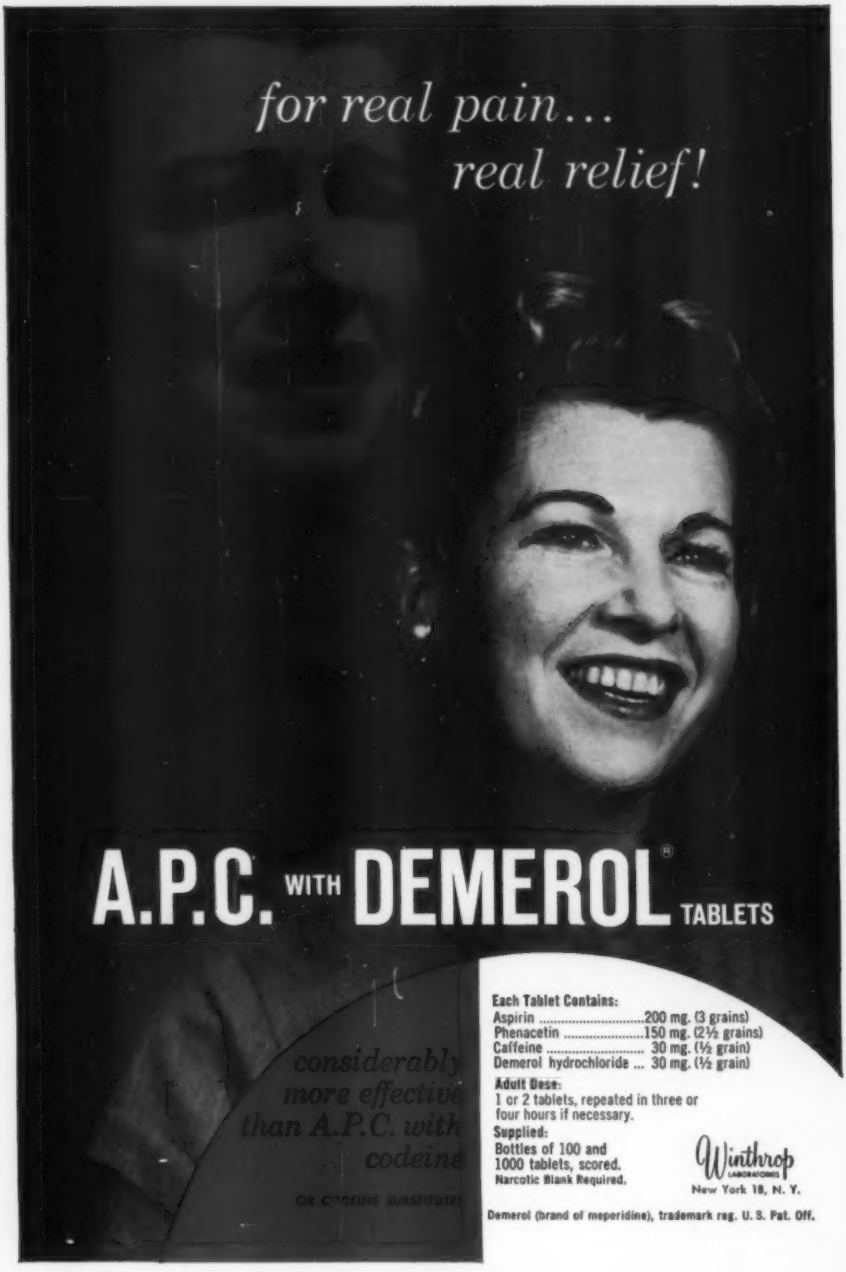

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